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Added sugar, sugar-sweetened foods and beverages and risk of pancreatic cancer in the NIH-AARP Diet and Health Study

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Abstract

Background—Although hyperglycemia, hyperinsulinemia and insulin resistance have been hypothesized to be involved in the development of pancreatic cancer, results from epidemiologic studies on added sugar intake are inconclusive.

Objective—Our objective was to investigate whether the consumption of total added sugar, sugar-sweetened foods and beverages is associated with pancreatic cancer risk.

Design—We prospectively examined 487922 men and women aged 50–71 years and free of cancer and diabetes in 1995–96. Total added dietary sugar intake in teaspoons per day (based on USDA's Pyramid Servings Database) was assessed with a food frequency questionnaire. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated with adjustment for total energy and potential confounding factors.

Results—During an average 7.2 years of follow-up, 1258 incident pancreatic cancer cases were ascertained. The median intakes for the lowest and highest quintiles of total added sugar intake were 12.6 g/day and 96.2 g/day. No overall increased risk of pancreatic cancer was observed in men or women with high intake of total added sugar or sugar-sweetened foods and beverages. For men and women combined, the multivariate RRs of the highest versus lowest intake categories were 0.85 (95% CI: 0.68, 1.06; P trend= 0.07) for total added sugar, 1.01 (95% CI: 0.82,1.23; P trend= 0.58) for sweets, 0.98 (95% CI: 0.82,1.18; P trend= 0.49) for dairy desserts, 1.12 (95% CI: 0.91,1.39; P trend= 0.35) for sugar added to coffee and tea, and 1.01 (95% CI: 0.77,1.31; P trend= 0.76) for sugar-sweetened soft drinks.

Conclusion—Our results do not support the hypothesis that consumption of added sugar, or sugar-sweetened foods and beverages is associated with overall risk of pancreatic cancer.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in the United States with a five-year survival rate of less than 5% and fatality rate of nearly 100% (1). Hyperglycemia and hyperinsulinemia have been shown to be important in the etiology of this malignancy,

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probably by the stimulatory effect of insulin on cell proliferation (2, 3). Many of the recognized risk factors for pancreatic cancer, including obesity and type 2 diabetes mellitus, have been related to abnormal glucose tolerance and insulin resistance (4–6). High sugar intake increases blood glucose and insulin response, which may contribute to a favorable environment for the development of pancreatic cancer (7).

Several prospective studies have investigated the influence of sugar or carbohydrate intake on risk of pancreatic cancer, but the findings are inconsistent, ranging from an inverse association (8) or no association (9–12) to a positive association (13, 14). In contrast, most case-control studies have shown a positive association with sugar or carbohydrate intake (15). Glycemic load, a quantitative measure of glycemic effect, was associated with increased risk of pancreatic cancer in the Nurses' Health Study (NHS) (13), whereas no association was found in other cohorts (9–12). Sugar-sweetened soft drink, the leading source of added sugars in the U.S. diet (16), has been linked with weight gain and type 2 diabetes (17) and to pancreatic cancer in one study (18).

These conflicting results could be partly due to relatively small numbers of cases (8–11, 13, 14, 18), inadequate control for diabetes (9) and incomplete exposure information (14), all of which may distort the true association between sugar consumption and the risk of pancreatic cancer. We therefore examined consumption of sugar, sugar-sweetened foods and beverages in relation to the risk of pancreatic cancer in the NIH-AARP Diet and Health Study, a large prospective cohort study of more than half a million US men and women with wide dietary intake distributions and detailed information on potential risk factors for pancreatic cancer.

SUBJECTS AND METHODS

Study population

Details of the NIH-AARP Diet and Health Study have been described elsewhere (19). Briefly, the cohort was initiated in 1995–1996 when a self-administered baseline food-frequency questionnaire (FFQ) was mailed to 3.5 million AARP members. The baseline questionnaire also collected information on participants' demographic characteristics and other potential cancer risk factors (e.g., smoking, physical activity, family history of cancer, medical conditions). Recipients were ages 50–71 years and resided in one of six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). Although the response rate to the baseline questionnaire was low (17.6 percent), it would not affect the internal validity of our study given the prospective design. Of the 617,119 individuals who returned the questionnaire, 567,169 respondents provided satisfactory dietary data. We excluded individuals with duplicate representation (n = 179), individuals who moved out of the study areas before returning the questionnaire (n = 321), died before study entry (n = 261), or withdrew (n = 6). From the remaining 566,402 participants, we excluded proxy respondents (n=15,760), prevalent cancer cases identified through cancer registries at baseline (n=8,583), those with history of diabetes (n= 49,817) as diabetic patients often reduce their sugar intake after diagnosis, and those with extreme energy intake (i.e., beyond two interquartile ranges from the median) (n=4,320). After these exclusions, the analytic cohort consisted of 487,922 participants (284,076 men and 203,846 women). The NIH–AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Cancer ascertainment

Incident cases of pancreatic cancer, through December 31, 2003, were identified through the eleven state cancer registries. In addition to the participants who resided in the eight initial

study areas, the participants who moved to Texas, Nevada, and Arizona were also followed-up for outcomes. We estimated that approximately 90 percent of all cancer cases in our cohort were validly identified using linkage to state cancer registries (20). Deaths from pancreatic cancer were additionally identified through the National Death Index. For our analyses, we included only incident cases of primary adenocarcinoma of the exocrine pancreas (International Classification of Diseases for Oncology, Third Edition, ICD-O-3 code C25.0-C25.3 and C25.7-C25.9). We excluded endocrine pancreatic tumors (ICD-O-3 code C25.4) because the etiology of these cancers is thought to be different (2).

Dietary assessment

Dietary intakes were derived from the baseline 124-item FFQ. Participants were queried about their usual frequency of consumption and portion size over the previous year, using ten categories of frequency ranging from never to 6 or more times per day for beverages and from never to 2 or more times per day for foods and three categories of portion size (19, 21). Participants were also asked whether they usually drank sugar-free (diet) or regular-calorie type of a particular beverage. From these responses, daily consumption of foods, beverages and nutrients were calculated using data from the US Department of Agriculture's (USDA) 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII) (21).

Total added sugar in teaspoons per day was defined by USDA's Pyramid Servings Database, which enabledus to estimate added sugar intake from all foods in the FFQ (22, 23). Added sugar included sugars that were eaten separately and sugars used as ingredients in processed or prepared foods. Naturally occurring sugars such as lactose in milk or the fructose in fruit were not included. One teaspoon of added sugar was defined as 4.2 grams of table sugar (sucrose) (23).

The performance of the FFQ was evaluated using two nonconsecutive 24-hour recalls among a subgroup of the cohort consisting of 2053 individuals (24). The energy-adjusted Pearson correlation coefficients for carbohydrate between the FFQ and the 24-hour recall were 0.71 (men) and 0.64 (women).

Statistical analysis

To facilitate analysis, sugar-sweetened foods and beverages were grouped into sugar-sweetened beverages (regular soft drinks and regular fruit drinks), sugar added to coffee and tea, sweets (candy, cookie, cake, pie, donut and sweet roll), dairy desserts (ice cream and frozen yogurt) and other sugar-sweetened foods (muffin, cornbread and pancake). Although total added sugar was derived from all foods in the FFQ, not all possible foods with added sugars were included in the food groups. Spearman correlation coefficients were computed among these sugar-sweetened food and beverage groups.

Consumption of total added sugar and sugar-sweetened food groups was analyzed in quintiles. This approach reduces the influence of extreme observations on the effect estimates. For analyses combining men and women, quintiles were based on the intake distribution of the entire cohort. For sex-specific analyses, quintiles were based on the sex-specific intake distributions. Due to the large number of participants who did not regularly consume sugar-sweetened beverages or sugar added to coffee/tea, they were assigned into the lowest intake quintile. We then evenly divided the remainder into four categories based on sex-specific intakes and treated them as quintiles 2 to 5. For total, regular and diet soft drink, we assigned never drinkers into the lowest categories and then divided the remainder into sex-specific quintiles. We used the lowest intake categories as the reference throughout the analyses.

We then estimated the power to detect a specified relative risk for the highest versus the lowest categories of intake of total added sugar, regular soft drink and diet soft drink with a two-sided α level at 0.05 (25).

Person-years of follow-up were calculated from the scan date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death, emigration out of the study areas, or December 31, 2003, whichever occurred first. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models with age as the primary time scale. The proportional hazards assumption was verified by modeling interaction terms of age and our main exposures as well as other fixed covariates.

We analyzed data by using two energy adjustment methods. Intakes of our main exposures were included as the absolute daily amount (standard model), or daily amount per 1000 kcal (density model). When the two methods yielded similar results, we only presented risk estimates for absolute daily amount to allow direct comparison with previous publications. In multivariate models, we considered adjusting for sex, race (Caucasian; Black; Hispanic; Asian, Pacific Islander or American Indian/Alaskan Native; and missing), education (≤ 11 years, 12 years or completed high school, post-high school or some college, college or post-graduate, and missing), body mass index (BMI kg/m^2, <18.5, 18.5 – <25, 25 – <30, 30 – <35, ≥ 35, and missing), alcohol (grams/day, quintiles), smoking (never, quit ≥ 10 years, quit 5 through 9 years ago; quit 1 through 4 years ago, quit < 1 year ago or current and smoked ≤ 20 or > 20 cigarettes/day; and missing), physical activity (never, rarely, <3 times/month, 1–2 times/week, 3–4 times/week, ≥5 times/week, and missing), total energy (continuous), energy adjusted total fat intake (quintiles), energy adjusted saturated fat intake (quintiles), energy adjusted red meat (quintiles), energy adjusted folate (quintiles) and use of multivitamins (yes/no). In the final multivariate models, we only kept those variables that altered the sugar-pancreatic cancer risk ratios by 5% or more. For sugar-sweetened beverages, we additionally adjusted for diet beverages consumption (never drinkers and quartiles of the remainder). Similarly, regular soft drink and diet soft drink were mutually adjusted. Since BMI may mediate the association between sugar and pancreatic cancer, we repeated our analysis without controlling for BMI. An indicator variable for missing values of each covariate was created. Linear trends were tested by the Wald test of a score variable that contained median values of intake categories.

We further conducted stratified analyses by strong risk factors of pancreatic cancer including sex and smoking (never smokers or quit ≥10 years versus current smokers or quit <10 years, as the previous study (26) showed that the risks of pancreatic cancer were similar for never smokers and former smokers who quit ≥10 years ago). Because individuals who are obese and individuals who are less active tend to have a greater insulin response to their diet compared with lean or active individuals (5, 18), we also examined whether the association of added sugar or soft drink with pancreatic cancer varied across strata of BMI (<30 versus ≥30 kg/m^2 and <35 versus ≥35 kg/m^2) and physical activity (<3 versus ≥3 times/week). Tests for interaction were performed by the likelihood ratio test comparing models with and without cross-product terms. To further examine whether the associations of our interest are more apparent among those with greater insulin resistance, we analyzed the associations among subgroups defined by the combination of BMI and physical activity.

In sensitivity analyses, we excluded the first 2 years of follow-up for all participants to rule out an effect of subclinical pancreatic cancer on added sugar intake. Because patients with cardiovascular disease or those with poor health might change their diet, we assessed their influence on the main study results in two additional sensitivity analyses: one that excluded those with heart disease at baseline (12.5% of the whole cohort) and a second restricted to those who reported their health status as excellent or very good (54.4% of the whole cohort).

In addition, we repeated our analyses by excluding, respectively, those who did not report smoking status, those who reported cancer history at baseline that were not recorded in cancer registries or those who had extreme intake of total added sugar. The estimates were similar to those of the main analysis. We additionally analyzed our main exposures in quartiles or categories defined by prespecified cutpoints of intakes, which also yielded consistent results with those based on quintiles. Analysis using reported frequencies of intake made little difference.

SAS statistical software (version 9.1; SAS Institute, Inc, Cary, NC) was used for all analyses. All statistical tests were two-sided; *p* values less than 0.05 were considered statistically significant.

RESULTS

During 3,521,088 person-years of follow-up (mean: 7.2 years), we identified 1,258 incident cases of pancreatic cancer (808 men and 450 women). For men and women combined, the median intakes for the lowest and highest quintiles of total added sugar intake were 3.0 teaspoons/day (12.6 g/day) and 22.9 teaspoons/day (96.2 g/day). Compared to those with low intake of total added sugar, individuals with high sugar intake were younger, of Black race or ethnic group, less educated, physically inactive, likely to smoke and consume more fat but less alcohol, folate and multivitamins (Table 1). Forty-eight percent of men and 36% of women were drinkers of regular soft drink; 42% of men and 49% of women were drinkers of diet soft drink. Individuals with high consumption of regular soft drinks generally had similar characteristics to those with high sugar intake. In contrast, individuals who drank diet soft drinks were more educated, less likely to smoke and consumed more folate and multivitamins than those who never drank diet soft drink.

Among all participants, intake of total added sugar was not associated with pancreatic cancer risk (Table 2: for the highest versus lowest quintile, RR=0.85; 95% CI: 0.68, 1.06; P trend= 0.07). Although women with the highest intake of total added sugar had a significantly reduced risk (RR=0.65; 95% CI: 0.44, 0.95; P trend=0.01), the association was attenuated and no longer of statistical significance after excluding the first 2 years of follow-up (RR=0.72; 95% CI: 0.47, 1.10; P trend=0.09). In addition, when examining energy-adjusted added sugar intake as teaspoons per 1000 kcal, no association was observed for men or women or men and women combined (data not shown).

In this population, the main food sources for total added sugar were sweets (25.7%), sugar-sweetened beverages (24.8%; 19.3% from regular soft drinks and 5.5% from regular fruit drink), dairy desserts (9.1%), and sugar added to coffee/tea (8.4%). Correlations between sugar-sweetened foods and beverages were weak, with Spearman correlation coefficients ranging from −0.01 to 0.34 (sweets with dairy desserts).

After adjustment for potential confounders, consumption of sugar-sweetened beverages, sugar added to coffee/tea, sweets, dairy desserts, and other sugar-sweetened foods showed no trends for pancreatic cancer risk (Table 2). Neither regular soft drink nor diet soft drink had a significant trend towards greater risk of pancreatic cancer (Table 3). Although risks were significantly increased for a few mid-quintiles of soft drink consumption, those increases were not monotonic across quintiles. Separate analyses among men or women showed similar associations (data not shown). The results for sugar-sweetened foods and beverages did not change after excluding the first 2 years of follow-up. Analyzing energy-adjusted intake as grams per 1000 kcal instead of absolute amount of sugar-sweetened foods and beverages had essentially no impact on the risk ratios (data not shown).

The above findings remained the same after removing BMI from the multivariate models, excluding those with heart disease, or restricting to those who reported their health status as excellent or very good (data not shown).

There was no statistical interaction between sex and intake of total added sugar or soft drinks (likelihood ratio test p=0.17 for total added sugar, p=0.75 for regular soft drink and p=0.24 for diet soft drink). For men and women combined, the associations between intake of added sugar or soft drinks and the risk of pancreatic cancer did not significantly vary across strata of BMI (<30 versus ≥30 kg/m^2), physical activity and smoking history (Table 4). Compared to non-obese women, women who were obese appeared to have higher risks of pancreatic cancer for total added sugar and regular soft drink but lower risk for diet soft drink. However, none of the risk estimates were significantly different from null (data not shown). In addition, interactions by BMI among women were not statistically significant (likelihood ratio test p=0.50 for total added sugar and p=0.38 for diet soft drink) or only borderline significant (p=0.05 for regular soft drink). Although p values were significant for interaction between total added sugar and physical activity among women (p=0.03) and interaction between diet soft drink and smoking among men (p=0.03), none of the risk estimates were statistically significantly (data not shown).

We further explored the associations stratified by BMI ≥35 kg/m^2 as the risk for pancreatic cancer is greatest at these BMI levels. For men and women combined, high intake of total added sugar was associated with a nonsignificant increase in pancreatic cancer risk among those with BMI ≥35 kg/m^2 (compared to the lower tertile, the middle tertile, RR=1.59, 95% CI: 0.80, 3.17 and the upper tertile, RR=1.83, 95% CI: 0.80, 4.19; P trend=0.20; the cases for lower, middle and upper tertiles were 16, 21 and 20). Similarly, among those with BMI≥35 kg/m^2 and physical activity<3 times/week, total added sugar also increased the risk of pancreatic cancer (compared to the lower tertile, the middle tertile, RR=2.70, 95% CI: 1.12, 6.52 and the upper tertile, RR=2.96, 95% CI: 1.05, 8.40; p trend=0.09; the cases for lower, middle and upper tertiles were 8, 17 and 16). Nevertheless, we lacked the statistic power due to small number of cases and sex-specific analyses showed no statistically significant associations (data not shown). Regular soft drink and diet soft drink were not associated with pancreatic cancer risk for those who were extremely obese or those who were both extremely obese and less active among men or women or combined (data not shown).

The risk estimates for subgroup analyses were virtually unchanged and the confidence intervals were wider after excluding the first 2 years of follow-up, excluding those with heart disease, or restricting to those who reported their health status as excellent or very good (data not shown).

DISCUSSION

In this large cohort of US men and women, we found no overall associations of total added sugar, sugar-sweetened foods and beverages with pancreatic cancer risk.

The lack of overall associations in the study is unlikely to be due to lack of statistical power. Given its large size, we had sufficient power (80%) in the study cohort to detect a moderate association between pancreatic cancer and the highest intake category of total added sugar (RR>1.26) and regular soft drink (RR>1.35). In addition, because of its prospective design and the completeness of follow-up, neither selection bias nor differential case ascertainment is likely to be responsible for the null findings.

Although misclassification of total added sugar and sweetened food consumption is inevitable as dietary intakes were self-reported, it is unlikely to attenuate the estimates

dramatically given the high correlation for carbohydrate observed in the validation study (24). The study ascertained histologically confirmed incident cases from eleven cancer registries with 90% completeness (20), indicating that the observed null associations are not likely to result from misclassification of pancreatic cancer cases.

Residual confounding by measured factors might be of minor importance in the present study as our age/sex-adjusted models and multivariable models yielded very similar results. Furthermore, although obesity might mediate the association between dietary intake and pancreatic cancer, the null relations are not likely to be the result of over controlling for BMI because our sensitivity analyses demonstrated that adjustment for BMI did not make any difference to the risk estimates.

One possible explanation for the lack of overall associations is that dietary intake might be changed by preclinical disease at baseline. To rule out the possibility of change in sugar intake due to undiagnosed pancreatic cancer, we excluded the first 2 years of follow-up for all participants in sensitivity analyses. The results were unchanged. Since patients with diabetes usually limited their sugar intake and thus would bias the estimates downward, we excluded from analysis those with history of diabetes at baseline so that the observed association of dietary intake with pancreatic cancer risk would not be due to pre-existed diabetes. In addition to diabetes, pre-diabetics status is another reason for people to change their diet and lifestyle. Therefore a change in dietary intake after diagnosis of pre-diabetes condition would result in measurement error (i.e., would not be representative of long-term diet) and thus might underestimate the true risk. Unfortunately, the influence of pre-diabetics condition cannot be eliminated from this study and could potentially explain a lack of association. We attempted to address this issue by restricting the analysis to those who reported their health status as excellent or very good; no changes in overall risk estimates were observed.

The lack of overall associations for added sugar intake and pancreatic cancer risk in this study is consistent with data from most prospective studies (9–12). Although high glycemic load and fructose were associated with a nonsignificant increase in pancreatic cancer risk in the Nurses' Health Study (NHS), the null relations observed for carbohydrate and sucrose in the same cohort is consistent with our findings (13). In contrast, carbohydrate was inversely associated with pancreatic cancer risk in Finnish male smokers (8). However, the Finnish diet, particularly during the mid-1980's, might not be comparable to the American diet, in that the carbohydrate consumed by the Finns did not tend to be from sweets or soft drinks as American populations but from a rye bread that had lots of fiber and phytochemicals (8). We failed to confirm the positive association reported in a recent prospective study in Sweden for ≥5 teaspoons/day of sugar added to coffee or tea (RR, 1.69; 95% CI: 0.99, 2.89) (14). Nevertheless, the Swedish study included only 131 cases of pancreatic cancer. In addition, as noticed by the Swedish investigators (14), the components or recipes of sweet foods and beverages in US and Swedish populations might be different which could make the two studies difficult to compare.

The association of soft drink intake with pancreatic cancer risk was examined in three previous cohort studies. The Multiethnic Cohort Study showed no association (12). The Swedish study found an elevated risk of pancreatic cancer for ≥2 glasses/day of total soft drink (RR, 1.93; 95% CI: 1.18, 3.14) (14). In addition to the limitations mentioned above, the information on the type of soft drink was not available in that study. In two US cohorts, women who consumed >3 drinks/week of sugar-sweetened soft drink appeared to have a significant increase in risk (RR, 1.57; 95% CI: 1.02, 2.41), whereas no association was observed among men (18). The main strength of that study is that the dietary intake was

cumulatively updated during 20 years of follow-up. We are uncertain whether the long follow-up and repeated dietary assessments could explain the different results obtained.

A few studies showed that the adverse effect of glycemic load, sucrose or regular soft drink consumption was more pronounced among those with greater insulin resistance (12, 13, 18). Although total added sugar intake was not associated with overall risk of pancreatic cancer in the present study, risks were elevated among those with BMI≥35 kg/m^2 and among those who were extremely obese as well as less active. Nonetheless, subgroup analyses increase the chance of false-positive findings and we lacked statistical power to detect these associations due to the small number of cases in the subgroups. Therefore, these findings should be interpreted with caution although we can not exclude the possibility of an increased risk among those with greater insulin resistance.

Several study limitations need to be considered. Dietary changes during the follow-up period cannot be addressed in our study because intakes were measured only at baseline. However, we do not expect that a significant number of participants in our analysis cohort would change their diet intake in such a relatively short follow-up period (average 7.2 years). On the other hand, if added sugar intake has a long latent period for pancreatic cancer, the short duration of follow-up is insufficient to detect the effects of long-term sugar intake. Unmeasured confounding by unknown factors cannot be completely ruled out; however, such confounding factors would have to be relatively prevalent, highly correlated with dietary intake in this cohort, and strong risk factors for pancreatic cancer in order to make a great impact. Although the cohort members appeared to have a healthier liftstyle compared to the general US population (19), the added sugar intake was comparable to the previous study (12). Finally, as our cohort is comprised of predominantly white men and women, our results may not be generalizable to other ethnic populations.

In conclusion, this large prospective cohort study suggests that total added sugar, sugar-sweetened foods and beverages do not raise the overall risk of pancreatic cancer. Further work is needed to confirm the effect modification by BMI and physical activity to elucidate the role of insulin resistance and provide a more in-depth understanding of the association.

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The authors' responsibilities were as follows—AS, AFS and AH contributed to the design and data collection; AFS and YP were responsible for data management; YB, DSM, RSS and LJ contributed to the statistical analysis; YB and DSM prepared the manuscript; RSS, LJ, DTS and MFL helped with the interpretation of results; all authors provided a critical review of the manuscript.

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Table 1

Baseline characteristics of NIH-AARP participants according to consumption of total added sugar, regular soft drink and diet soft drink[1]

	Total added sugar			Regular soft drink				Diet soft drink			
Category	**Quintile 1**	**Quintile 3**	**Quintile 5**	**Never**	**Quintile 1**	**Quintile 3**	**Quintile 5**	**Never**	**Quintile 1**	**Quintile 3**	**Quintile 5**
Men (n = 284 076)											
Median intake[2]	3.3	9.3	25.1	0	12.1	77.0	537.2	0	17.2	168.7	820.4
No. of participants	56874	56743	56827	146869	25745	27987	27595	164119	24772	24498	24342
Age (y)	62.5 ± 5.3 [3]	62.5 ± 5.3	61.3 ± 5.5	62.3 ± 5.3	63.2 ± 5.1	62.2 ± 5.4	60.5 ± 5.5	62.3 ± 5.4	63.1 ± 5.1	62.4 ± 5.2	60.4 ± 5.4
African American (%)	1.8	2.1	3.9	1.4	2.4	3.9	4.3	3.3	1.3	1.2	1.0
Education (% > college degree)	50.7	48.3	34.2	49.9	46.5	41.7	33.8	41.5	54.3	51.2	47.3
BMI (kg/m^2)	27.2 ± 4.2	27.0 ± 4.1	27.1 ± 4.3	27.5 ± 4.3	26.0 ± 3.7	26.7 ± 4.0	27.1 ± 4.3	26.6 ± 4.0	27.0 ± 4.0	27.6 ± 3.9	28.7 ± 4.6
Physical activity (%≥ 5 times/week)	21.8	22.0	20.3	24.0	21.6	18.1	18.5	20.3	25.2	22.8	22.3
Currently smoking (%)	7.5	8.8	17.3	7.6	12.2	12.2	17.4	13.2	6.6	5.7	8.4
Diet											
Total energy (kcal/day)	1446.1 ± 626.7	1960.5 ± 661.1	2741.8 ± 930.8	1904.6 ± 786.3	1929.6 ± 803.5	2075.3 ± 829.4	2555.7 ± 978.7	2109.7 ± 883.6	1777.4 ± 716.7	1840.1 ± 704.0	2087.3 ± 863.2
Total fat (g/1000 kcal per day)	31.6 ± 9.4	33.7 ± 8.3	34.6 ± 8.0	32.8 ± 8.7	33.2 ± 9.0	35.2 ± 8.0	33.0 ± 7.9	33.9 ± 8.5	31.0 ± 8.4	33.1 ± 8.0	34.7 ± 8.9
Saturated fat (g/1000 kcal per day)	9.5 ± 3.4	10.5 ± 3.2	11.3 ± 3.2	10.1 ± 3.3	10.5 ± 3.6	11.2 ± 3.2	10.7 ± 3.1	10.8 ± 3.4	9.4 ± 3.1	10.1 ± 3.0	10.8 ± 3.3
Red meat (g/1000 kcal per day)	36.3 ± 24.0	36.8 ± 21.5	38.6 ± 20.5	36.1 ± 22.5	34.3 ± 21.5	39.6 ± 21.0	39.6 ± 20.6	37.4 ± 21.7	32.3 ± 20.8	37.2 ± 21.3	41.3 ± 24.1
Total folate (mcg/1000 kcal per day)	248.3 ± 77.2	232.4 ± 62.9	188.3 ± 51.9	238.9 ± 68.7	232.6 ± 69.3	217.0 ± 58.5	179.4 ± 53.0	217.0 ± 66.8	248.5 ± 70.5	238.9 ± 63.3	224.6 ± 64.7
Alcohol (g/day)[4]	7.3	4.3	2.1	4.7	5.1	3.8	2.1	3.7	6.0	5.2	2.8
Multivitamin (%)	53.2	53.4	48.8	55.2	51.4	49.6	46.6	49.8	56.8	55.7	55.3
Women (n = 203 846)											
Median intake[2]	2.8	7.3	19.4	0	7.4	44.5	469.4	0	11.7	160.4	816.2
No. of participants	40744	40812	40788	130513	13720	12824	14541	103991	19908	21800	18213
Age (y)	62.2 ± 5.4	62.0 ± 5.4	61.2 ± 5.5	62.0 ± 5.4	62.8 ± 5.2	62.0 ± 5.4	60.1 ± 5.4	62.2 ± 5.4	62.7 ± 5.2	61.9 ± 5.3	60.2 ± 5.4
African American (%)	3.4	4.1	8.6	3.1	5.0	8.1	11.9	6.7	2.6	3.6	2.9
Education (% > college degree)	32.8	33.1	23.4	33.0	31.1	26.3	21.5	28.3	34.9	32.3	29.9
BMI (kg/m^2)	26.1 ± 5.6	26.4 ± 5.6	27.1 ± 6.2	26.6 ± 5.8	25.2 ± 5.5	26.2 ± 5.6	27.5 ± 6.3	25.9 ± 5.9	26.0 ± 5.2	27.1 ± 5.6	28.3 ± 6.3
Physical activity (%≥ 5 times/week)	17.3	17.2	13.9	18.1	16.5	13.4	11.3	15.9	20.0	16.6	14.9
Currently smoking (%)	14.6	11.9	20.3	12.3	14.4	16.5	24.7	17.4	10.1	9.2	16.8
Diet											

	Total added sugar			Regular soft drink				Diet soft drink			
Category	**Quintile 1**	**Quintile 3**	**Quintile 5**	**Never**	**Quintile 1**	**Quintile 3**	**Quintile 5**	**Never**	**Quintile 1**	**Quintile 3**	**Quintile 5**
Total energy (kcal/day)	1066.5 ± 395.4	1525.2 ± 476.8	2181.7 ± 744.7	1497.1 ± 609.7	1513.4 ± 609.5	1623.6 ± 647.4	2017.1 ± 802.5	1636.1 ± 691.2	1395.2 ± 550.3	1481.6 ± 573.0	1626.1 ± 692.4
Total fat (g/1000 kcal per day)	32.5 ± 9.4	33.0 ± 8.4	33.9 ± 8.3	32.5 ± 8.7	33.3 ± 8.8	35.2 ± 8.2	32.9 ± 8.3	33.5 ± 8.9	30.9 ± 8.3	32.7 ± 8.0	34.6 ± 8.8
Saturated fat (g/1000 kcal per day)	9.7 ± 3.4	10.2 ± 3.2	10.9 ± 3.3	10.0 ± 3.2	10.4 ± 3.5	11.1 ± 3.3	10.5 ± 3.2	10.5 ± 3.5	9.4 ± 3.1	9.9 ± 2.9	10.7 ± 3.3
Red meat (g/1000 kcal per day)	29.8 ± 21.2	28.7 ± 18.9	29.3 ± 17.8	28.3 ± 19.4	26.0 ± 17.9	31.1 ± 18.7	32.3 ± 18.6	28.5 ± 19.1	25.2 ± 17.6	29.7 ± 18.2	33.8 ± 21.3
Total folate (mcg/1000 kcal per day)	265.8 ± 81.6	248.3 ± 64.4	201.6 ± 56.6	251.5 ± 71.1	250.2 ± 70.2	232.2 ± 61.9	183.8 ± 56.5	235.6 ± 73.7	260.6 ± 71.2	249.3 ± 63.7	233.2 ± 66.5
Alcohol (g/day)[4]	1.3	1.1	0.7	1.1	0.8	0.9	0.5	0.8	1.1	1.2	0.9
Multivitamin (%)	60.3	62.5	58.5	62.9	60.2	58.0	54.1	58.9	64.8	63.9	60.7

[1] P for trend < 0.01 for all variables except red meat intake across categories of total added sugar consumption in women (P=0.36) and physical activity across categories of diet soft drink consumption in women (P=0.35), according to the Cochran-Armitage tests for categorical variables and the t test for slope in linear regression models for continuous variables.

[2] Total added sugar (teaspoons/day), regular/diet soft drink (grams/day).

[3] Mean ± SD (all such values).

[4] Median intake.

Table 2

Relative risks and 95% confidence intervals for pancreatic cancer according to consumption of total added sugar, sugar-sweetened beverages and foods

	Quintiles[1]					
	1	2	3	4	5	P for trend
Total added sugar_pyramid servings						
Median intake (range)[2]	3.0 (0.1–4.3)	5.5 (4.4–6.8)	8.4 (6.9–10.2)	12.6 (10.3–16.1)	22.9 (16.2–240.2)	
Cases/person-years	247/702 900	260/704 797	245/706 027	256/705 592	250/701 773	
Age- and sex-adjusted RR	1.0	1.04 (0.88, 1.24)	0.98 (0.82, 1.17)	1.02 (0.86, 1.22)	1.06 (0.89, 1.27)	0.55
Multivariate RR[3]	1.0	1.04 (0.88, 1.25)	0.95 (0.79, 1.14)	0.93 (0.77, 1.13)	0.85 (0.68, 1.06)	0.07
Multivariate RR, 2 year lag[4]	1.0	1.06 (0.87, 1.30)	0.98 (0.80, 1.20)	0.94 (0.76, 1.17)	0.94 (0.74, 1.20)	0.41
Sugar-sweetened beverages[5]						
Median intake (range)[2]	0	10.5 (0.1–17.0)	27.2 (17.1–66.2)	134.0 (66.3–234.5)	430.9 (234.6–9948.7)	
Cases/person-years	574/1 599 213	146/482 092	187/473 998	200/486 494	151/479 291	
Age- and sex-adjusted RR	1.0	0.82 (0.68, 0.99)	1.05 (0.87, 1.26)	1.10 (0.92, 1.33)	0.95 (0.77, 1.16)	0.94
Multivariate RR[3]	1.0	0.82 (0.68, 0.99)	1.04 (0.86, 1.25)	1.07 (0.89, 1.30)	0.83 (0.67, 1.04)	0.10
Multivariate RR, 2 year lag[4]	1.0	0.84 (0.68, 1.03)	1.02 (0.83, 1.26)	1.07 (0.86, 1.32)	0.92 (0.72–1.17)	0.57
Sugar added to coffee/tea						
Median intake (range)[2]	0	3.9 (0.1–7.6)	9.4 (7.7–17.7)	19.4 (17.8–20.8)	34.8 (20.9–108.4)	
Cases/person-years	918/2 604 554	68/234 037	75/223 693	94/229 999	103/228 804	
Age- and sex-adjusted RR	1.0	0.90 (0.70, 1.15)	0.93 (0.74, 1.18)	1.16 (0.94, 1.43)	1.32 (1.08, 1.62)	0.01
Multivariate RR[3]	1.0	0.90 (0.70, 1.16)	0.90 (0.71, 1.15)	1.02 (0.82, 1.27)	1.12 (0.91, 1.39)	0.35
Multivariate RR, 2 year lag[4]	1.0	0.98 (0.75, 1.29)	0.91 (0.69, 1.18)	1.05 (0.83, 1.34)	1.17 (0.93, 1.48)	0.22
Sweets[5]						
Median intake (range)[2]	5.1 (0–8.7)	12.6 (8.8–16.9)	22.4 (17.0–29.3)	38.6 (29.4–52.6)	80.1 (52.7–1092.0)	
Cases/person-years	230/703 204	276/699 973	228/709 696	254/704 016	270/704 199	
Age- and sex-adjusted RR	1.0	1.20 (1.01, 1.43)	0.96 (0.80, 1.16)	1.06 (0.89, 1.27)	1.12 (0.94, 1.34)	0.46
Multivariate RR[3]	1.0	1.19 (0.99, 1.42)	0.94 (0.78, 1.13)	1.01 (0.84, 1.23)	1.01 (0.82, 1.23)	0.58
Multivariate RR, 2 year lag[4]	1.0	1.15 (0.95, 1.41)	0.89 (0.72, 1.10)	0.97 (0.79, 1.20)	0.94 (0.75, 1.17)	0.31
Dairy Desserts[5]						

	Quintiles[1]					
	1	2	3	4	5	P for trend
Median intake (range)[2]	1.3 (0–3.2)	4.6 (3.3–7.6)	10.0 (7.7–13.4)	26.1 (13.5–32.6)	65.9 (32.7–1127.4)	
Cases/person-years	251/704 126	244/702 132	274/709 268	236/703 619	253/701 944	
Age- and sex-adjusted RR	1.0	0.98 (0.82, 1.17)	1.08 (0.91, 1.28)	0.93 (0.78, 1.11)	0.97 (0.81, 1.16)	0.50
Multivariate RR[3]	1.0	1.01 (0.84, 1.20)	1.11 (0.93, 1.32)	0.96 (0.80, 1.15)	0.98 (0.82, 1.18)	0.49
Multivariate RR, 2 year lag[4]	1.0	1.07 (0.88, 1.31)	1.18 (0.97, 1.43)	1.02 (0.83, 1.25)	1.00 (0.82, 1.24)	0.43
Other sugar-sweetened foods[5]						
Median intake (range)[2]	0.7 (0–1.2)	2.0 (1.3–3.1)	3.8 (3.2–5.5)	7.6 (5.6–9.4)	19.4 (9.5–379.9)	
Cases/person-years	244/699 288	245/699 380	252/707 061	263/727 849	254/687 509	
Age- and sex-adjusted RR	1.0	1.03 (0.86, 1.23)	1.03 (0.87, 1.23)	1.01 (0.85, 1.21)	1.01 (0.85, 1.21)	0.92
Multivariate RR[3]	1.0	1.04 (0.87, 1.24)	1.05 (0.88, 1.26)	1.02 (0.85, 1.22)	1.00 (0.83, 1.20)	0.75
Multivariate RR, 2 year lag[4]	1.0	1.07 (0.88, 1.31)	1.02 (0.84, 1.25)	1.03 (0.85, 1.26)	1.01 (0.82, 1.24)	0.80

[1] For sugar-sweetened beverages and sugar added to coffee/tea, never drinkers were assigned into the lowest intake category. The remainder was divided into quartiles.

[2] Grams/day, except for total added sugar (teaspoons/day).

[3] Standard multivariable Cox regression models using age as the underlying time metric adjusted for sex, race (Caucasian; Black; Hispanic; Asian, Pacific Islander or American Indian/Alaskan Native; and missing), education (≤ 11 years, 12 years or completed high school, post-high school or some college, college or post-graduate, and missing), BMI (kg/m^2, <18.5, 18.5 – <25, 25 – <30, 30 –<35, ≥ 35, and missing), alcohol (quintiles), smoking (never, quit ≥ 10 years, quit 5 through 9 years ago; quit 1 through 4 years ago, quit < 1 year ago or current and smoked ≤ 20 or > 20 cigarettes/day; and missing), physical activity (never, rarely, <3 times/month, 1–2 times/week, 3–4 times/week, ≥5 times/week, and missing), energy adjusted red meat (quintiles), energy adjusted folate (quintiles) and total energy (continuous). For sugar-sweetened beverages, we additionally adjusted for diet beverages consumption (never drinkers and quartiles).

[4] Analysis excluded the first two years of follow-up. Cases/person-years in lag analysis: 657 cases/1 478 664 person-years (men) and 357 cases/1 078 172 person-years(women).

[5] Sugar-sweetened beverages included regular soft drinks and regular fruit drink. Sweets included candy, cookie, cake, pie, donut and sweet roll. Dairy desserts included ice cream and frozen yogurt. Other sugar-sweetened foods included muffin, combread and pancake.

Table 3

Relative risks and 95% confidence intervals for pancreatic cancer according to consumption of regular soft drink and diet soft drink

		Quintiles of drinkers					
	Never drinkers	**1**	**2**	**3**	**4**	**5**	**P for trend**
Total soft drink							
Median intake (range)[1]	0	11.8 (0.1–17.2)	27.2 (17.3–74.4)	105.5 (74.5–170.9)	261.7 (171.0–354.4)	816.9 (354.5–4974.1)	
Cases/person-years	147/418 382	224/609 117	237/674 387	207/575 404	241/628 993	202/614 806	
Age- and sex-adjusted RR	1.0	1.08 (0.88, 1.33)	1.04 (0.84, 1.27)	1.08 (0.87, 1.33)	1.21 (0.99, 1.49)	1.15 (0.93, 1.43)	0.19
Multivariate RR[2]	1.0	1.11 (0.90, 1.37)	1.07 (0.87, 1.32)	1.11 (0.90, 1.38)	1.21 (0.98, 1.50)	1.07 (0.86, 1.33)	0.95
Multivariate RR, 2 year lag[3]	1.0	1.15 (0.91, 1.46)	1.07 (0.84, 1.35)	1.13 (0.90, 1.44)	1.32 (1.04, 1.66)	1.17 (0.91, 1.49)	0.35
Regular soft drink							
Median intake (range)[1]	0	12.0 (0.1–12.9)	27.0 (13.0–32.4)	76.6 (32.5–107.9)	173.8 (108.0–289.9)	512.8 (290.0–4974.1)	
Cases/person-years	687/2 004 852	110/325 440	115/286 687	119/291 240	126/311 158	101/301 711	
Age- and sex-adjusted RR	1.0	0.97 (0.76, 1.24)	1.15 (0.90, 1.47)	1.21 (0.95, 1.54)	1.23 (0.97, 1.56)	1.16 (0.90, 1.49)	0.15
Multivariate RR[2]	1.0	0.97 (0.76, 1.24)	1.14 (0.89, 1.45)	1.20 (0.94, 1.53)	1.17 (0.92, 1.49)	1.01 (0.77, 1.31)	0.76
Multivariate RR, 2 year lag[3]	1.0	1.05 (0.80, 1.38)	1.18 (0.90, 1.55)	1.19 (0.90, 1.57)	1.24 (0.95, 1.63)	1.13 (0.84, 1.51)	0.60
Diet soft drink							
Median intake (range)[1]	0	15.9 (0.1–26.3)	74.4 (26.4–76.9)	167.9 (77.0–258.9)	350.9 (259.0–494.4)	816.9 (494.5–4897.6)	
Cases/person-years	716/927 936	137/360 163	86/280 990	99/310 106	118/325 501	102/316 392	
Age- and sex-adjusted RR	1.0	1.14 (0.90, 1.43)	0.91 (0.70, 1.18)	0.96 (0.75, 1.24)	1.17 (0.92, 1.49)	1.14 (0.89, 1.47)	0.46
Multivariate RR[2]	1.0	1.23 (0.97, 1.55)	0.97 (0.74, 1.27)	1.03 (0.80, 1.33)	1.23 (0.96, 1.56)	1.11 (0.86, 1.44)	0.68
Multivariate RR, 2 year lag[3]	1.0	1.22 (0.94, 1.59)	1.00 (0.74, 1.35)	1.00 (0.75, 1.34)	1.35 (1.03, 1.77)	1.25 (0.94, 1.66)	0.19

[1] Grams/day.

[2] Standard multivariable Cox regression models using age as the underlying time metric adjusted for sex, race (Caucasian; Black; Hispanic; Asian, Pacific Islander or American Indian/Alaskan Native; and missing), education (≤ 11 years, 12 years or completed high school, post-high school or some college, college or post-graduate, and missing), BMI (kg/m^2, <18.5, 18.5 – <25, 25 – <30, 30 – <35, ≥ 35, and missing), alcohol (quintiles), smoking (never, quit ≥ 10 years, quit 5 through 9 years ago; quit 1 through 4 years ago, quit < 1 year ago or current and smoked ≤ 20 or > 20 cigarettes/day; and missing), physical activity (never, rarely, <3 times/month, 1–2 times/week, 3–4 times/week, ≥5 times/week, and missing), energy adjusted red meat (quintiles), energy adjusted folate (quintiles) and total energy (continuous). Regular soft drink and diet soft drink were mutually adjusted.

[3] Analysis excluded the first two years of follow-up. Cases/person-years in lag analysis: 657 cases/1 478 664 person-years (men) and 357 cases/1 078 172 person-years(women).

Table 4

Relative risks and 95% confidence intervals for pancreatic cancer according to consumption of total added sugar, regular soft drink and diet soft drink, stratified by BMI, physical activity, and smoking status[1]

	Cases[2]	Quintiles of intake[3]					P for trend
		1	2	3	4	5	
Total added sugar							
Median intake[4]		3.0	5.5	8.4	12.6	22.9	
Nonobese (BMI < 30 kg/m^2)	998	1.0	1.06 (0.87, 1.29)	0.91 (0.74, 1.12)	0.91 (0.74, 1.13)	0.86 (0.67, 1.10)	0.13
Obese (BMI ≥ 30 kg/m^2)	231	1.0	1.02 (0.68, 1.54)	1.06 (0.69, 1.61)	1.04 (0.67, 1.62)	0.78 (0.45, 1.33)	0.28
P value for interaction							0.49
High physical activity[5]	561	1.0	0.99 (0.77, 1.27)	0.88 (0.67, 1.15)	0.83 (0.63, 1.11)	0.71 (0.50, 1.00)	0.03
Low physical activity[5]	688	1.0	1.09 (0.85, 1.39)	1.01 (0.78, 1.30)	1.02 (0.79, 1.33)	0.95 (0.70, 1.27)	0.49
P value for interaction							0.06
Never smoker or quit ≥ 10 y	775	1.0	1.13 (0.91, 1.41)	0.89 (0.71, 1.13)	0.95 (0.74, 1.22)	0.87 (0.65, 1.17)	0.18
Current smoker or quit < 10 y	423	1.0	0.97 (0.70, 1.35)	1.07 (0.80, 1.48)	0.98 (0.71, 1.36)	0.85 (0.59, 1.21)	0.26
P value for interaction							0.44
Regular soft drink							
Median intake[4]		0	12.1	27.2	171.0	364.3	
Nonobese (BMI < 30 kg/m^2)	998	1.0	0.99 (0.76, 1.28)	1.17 (0.91, 1.49)	1.21 (0.94, 1.56)	0.91 (0.68, 1.20)	0.34
Obese (BMI ≥ 30 kg/m^2)	231	1.0	0.73 (0.37, 1.44)	1.23 (0.70, 2.15)	0.92 (0.50, 1.69)	1.26 (0.71, 2.24)	0.29
P value for interaction							0.28
High physical activity[5]	561	1.0	0.93 (0.66, 1.32)	1.04 (0.74, 1.46)	1.06 (0.75, 1.50)	0.89 (0.60, 1.33)	0.63
Low physical activity[5]	688	1.0	1.01 (0.73, 1.40)	1.36 (1.00, 1.84)	1.28 (0.94, 1.75)	1.03 (0.74, 1.44)	0.63
P value for interaction							0.44
Never smoker or quit ≥ 10 y	775	1.0	1.07 (0.79, 1.46)	1.20 (0.89, 1.62)	1.05 (0.76, 1.43)	1.10 (0.79, 1.54)	0.96
Current smoker or quit < 10 y	423	1.0	0.83 (0.56, 1.24)	1.28 (0.90, 1.83)	1.24 (0.85, 1.79)	0.88 (0.59, 1.30)	0.44
P value for interaction							0.94
Diet soft drink							
Median intake[4]		0	16.2	74.8	260.6	816.9	
Nonobese (BMI < 30 kg/m^2)	998	1.0	1.31 (1.03, 1.68)	0.88 (0.67, 1.17)	1.20 (0.93, 1.56)	1.16 (0.88, 1.53)	0.59

	Cases[2]	Quintiles of intake[3]					
		1	2	3	4	5	P for trend
Obese (BMI ≥ 30 kg/m^2)	231	1.0	0.91 (0.51, 1.63)	0.94 (0.53, 1.64)	0.93 (0.54, 1.61)	0.89 (0.51, 1.53)	0.73
P value for interaction							0.06
High physical activity[5]	561	1.0	1.21 (0.89, 1.66)	0.87 (0.61, 1.23)	1.01 (0.72, 1.41)	1.14 (0.81, 1.62)	0.52
Low physical activity[5]	688	1.0	1.27 (0.92, 1.75)	1.04 (0.74, 1.47)	1.27 (0.92, 1.76)	1.12 (0.79, 1.57)	0.84
P value for interaction							0.65
Never smoker or quit ≥ 10 y	775	1.0	1.22 (0.92, 1.64)	1.03 (0.76, 1.40)	1.11 (0.82, 1.49)	1.25 (0.92, 1.71)	0.32
Current smoker or quit < 10 y	423	1.0	1.21 (0.81, 1.79)	0.80 (0.51, 1.27)	1.19 (0.80, 1.79)	0.92 (0.60, 1.40)	0.45
P value for interaction							0.31

[1] For regular soft drink and diet soft drink, never drinkers were assigned into the lowest intake category. The remainder was divided into quartiles.

[2] Standard multivariable Cox regression models adjusted for sex, race (Caucasian; Black; Hispanic; Asian, Pacific Islander or American Indian/Alaskan Native; and missing), education (≤ 11 years, 12 years or completed high school, post-high school or some college, college or post-graduate, and missing), BMI (kg/m^2, <18.5, 18.5 – <25, 25 – <30, 30 – <35, ≥ 35, and missing), alcohol (quintiles), smoking (never, quit ≥ 10 years, quit 5 through 9 years ago; quit 1 through 4 years ago, quit < 1 year ago or current and smoked ≤ 20 or > 20 cigarettes/day; and missing), physical activity (never, rarely, <3 times/month, 1–2 times/week, 3–4 times/week, ≥5 times/week, and missing), energy adjusted red meat (quintiles), energy adjusted folate (quintiles) and total energy (continuous). Regular soft drink and diet soft drink were mutually adjusted.

[3] Cases do not add up to 1258 because of missing information on stratification factors.

[4] Total added sugar (teaspoons/day), regular/diet soft drink (grams/day).

[5] High physical activity: ≥ 3 times/week; low physical activity: < 3 times/week.