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Predictors of fasting serum insulin and glucose and the risk of pancreatic cancer in smokers

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Abstract

Objectives—A history of type 2 diabetes is one of few consistent risk factors for pancreatic cancer. Potentially modifiable factors related to fasting insulin and glucose concentrations may influence pancreatic cancer risk.

Methods—Multiple linear regression models were used to identify anthropometric, clinical, behavioral, and dietary factors associated with fasting insulin and glucose in a subcohort of non-diabetics in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (n=366). Hazards ratios (HRs) and 95% confidence intervals (CIs) were calculated among the larger cohort (n=27,035).

Results—During follow-up (median 16.1 years), 305 participants developed pancreatic cancer. Fasting insulin and/or glucose were positively associated with body mass index (BMI), height, and dietary total and saturated fat and inversely associated with serum high-density lipoprotein cholesterol (HDL) and dietary available carbohydrates, sucrose, and alcohol. Comparing highest to lowest quintiles, total fat (HR=1.54, 95% CI 1.05–2.25, p-trend=0.01) and saturated fat (HR=1.38, 95% CI 0.97–1.98, p-trend=0.06) were positively associated and available carbohydrates (HR=0.63, 95% CI 0.44–0.90, p-trend=0.01), particularly sucrose (HR=0.62, 95% CI 0.43–0.89, p-trend=0.09) were inversely associated with risk of pancreatic cancer. BMI, HDL, height, and alcohol were not associated with pancreatic cancer risk.

Conclusion—Dietary fat is associated with higher fasting insulin concentrations and may increase pancreatic cancer risk in smokers.

Keywords

Insulin resistance; pancreatic cancer; lifestyle factors; nutrition; anthropometry

Pancreatic cancer ranks fourth and second as a cause of cancer mortality in the United States (1) and Finland (2), respectively, being highly fatal with a five-year survival of 5% (1). However, despite a large number of studies on the etiology of pancreatic cancer, few consistent risk factors have been identified. Cigarette smoking is the most well-established risk factor for

pancreatic cancer (3–4), but exposure to tobacco smoke may explain less than 30% of pancreatic cancer incidence (4). Long-term exposure to elevated concentrations of insulin may also play a role in pancreatic carcinogenesis (5–6). In addition to type 2 diabetes (7) and elevated concentrations of fasting (8–11) and postprandial (12) glucose, prospective studies have shown that elevated fasting insulin (10) and non-fasting c-peptide (a marker for insulin secretion) are associated with increased pancreatic cancer risk (13). Obesity strongly predicts hyperinsulinemia and diabetes (14) and has been associated with pancreatic cancer risk in numerous epidemiologic studies (3,15). However, few studies have reported associations of other lifestyle factors that may be mediated by insulin concentrations, such as physical activity (16–17), elevated blood pressure (17), or diet (16–20), with pancreatic cancer risk.

We previously reported a close to 2-fold increased pancreatic cancer risk with increasing insulin and glucose concentrations, as well as insulin resistance, in the Alpha-Tocopherol, Beta-Carotene Study (ATBC) of male smokers, that became stronger with longer follow-up (10). The first aim of our present investigation was to identify potentially modifiable factors associated with fasting serum insulin and glucose concentrations among non-diabetics from a sub-cohort of the ATBC Study. The second was to examine whether the identified factors were associated with risk of incident pancreatic cancer. Together, these analyses may identify potentially modifiable risk factors for pancreatic cancer that may explain the associations with higher insulin and glucose concentrations and diabetes that were previously observed in the ATBC Study (10) and other prospective studies (8–13). Our study updates previous findings from the ATBC Study (21–23), but includes nearly seven more years of follow-up and twice as many cases.

MATERIALS AND METHODS

Study Population

The ATBC Study, a randomized, double-blind, placebo-controlled, 2x2 factorial primary prevention trial, was designed to test the hypothesis that supplementation by alpha-tocopherol or beta-carotene decreases the risk of cancer (24). Briefly, men in southwestern Finland were eligible to participate in the trial if they were between the ages of 50 and 69 and smoked at least five cigarettes per day. Between 1985 and 1988, 29,133 men were randomized to either the intervention (supplemental alpha-tocopherol 50 mg/day, beta-carotene 20 mg/day, or both) or placebo group. Men who had a history of malignancy other than non-melanoma cancer of the skin or carcinoma *in situ*, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, or other medical conditions that might limit long-term participation, or who received anticoagulant therapy or used vitamin E (>20 mg/day), vitamin A (>20,000 IU/day), or beta-carotene (>6 mg/day) supplements were excluded from the trial. All participants provided written informed consent. The study was approved by the institutional review boards of the National Public Health Institute in Finland and the United States National Cancer Institute.

Follow-up and outcome ascertainment

The Finnish Cancer Registry provides nearly 100% case ascertainment in Finland (25). Deaths were verified through the Central Population Register, and death certificates were reviewed for the underlying cause of death. For pancreatic cancer cases diagnosed through April 1999, the medical records of these participants were reviewed by two study physicians for diagnostic confirmation. After April 1999, only information from the Finnish Cancer Registry on cancer cases was available. Only cases classified as primary pancreatic adenocarcinoma (ICD-9 code 157) were used in the analysis. Islet cell carcinomas (157.4) were excluded because they may have a different etiology from exocrine tumors.

Although the trial ended in April 1993 (median: 6.1 years of follow-up), cancer and mortality outcomes continue to be collected. Follow-up for the present analysis continued through April 30, 2004 or until death, representing follow-up of up to 19.4 years (median: 16.1 years) and 397,081 total person-years of observation. During follow-up, 319 participants developed incident exocrine pancreatic cancer. We excluded fourteen cases with missing dietary (n=13) and serum cholesterol (n=1) values. In total, 305 cases had complete relevant baseline information.

Exposure assessment

Prior to randomization, participants completed questionnaires regarding general background and demographics, medical history, physical activity, cigarette smoking, and occupation. Trained, registered nurses obtained standardized clinical measurements, such as height, weight, and blood pressure. Participants completed a self-administered food frequency questionnaire of 276 food items, designed specifically for the ATBC study, with the aid of color picture booklet to illustrate portion sizes. Dietary data were linked to a food composition database at the National Public Health Institute (<http://www.fineli.fi/>). These methods were validated among 190 pilot study participants using 24 days of food records spread over six months. Reproducibility of the food frequency questionnaire was examined among 121 different pilot study participants who repeated the questionnaire three times in the course of six months. Pearson correlation coefficients between the questionnaire and food records for energy-adjusted total fat, saturated fat, carbohydrates, and protein were 0.39, 0.62, 0.55, and 0.63, respectively. Intraclass correlations for total fat, saturated fat, carbohydrates, and protein were 0.64, 0.67, 0.70, 0.66, respectively (26).

Biomarkers

Fasting serum samples were collected from trial participants at baseline. Serum cholesterol, including high-density lipoprotein (HDL) cholesterol, was measured on each cohort member. In 2000, frozen serum samples from a random sample of cohort members (ATBC subcohort, n=400) who were alive without cancer during the first five years of follow-up were assayed for insulin and glucose concentrations as described previously (10). Quality controls had coefficient of variation (CV) percentages of 2.46% for glucose and 4.83% for insulin.

Statistical analysis

Linear regression models—The associations of lifestyle factors, including physical activity, serum HDL-cholesterol, BMI, height, systolic and diastolic blood pressure, dietary intakes of total and saturated fat, protein, fiber, alcohol, sucrose, starch, and available carbohydrates with fasting serum insulin and glucose concentrations were examined among participants in the ATBC subcohort who had complete dietary information and no self-reported history of diabetes at baseline (n=366). Linear regression was used to estimate mean changes and 95% confidence intervals (CIs) in insulin and glucose concentrations per unit change in the covariates. To preserve the assumption of normality in linear regression, insulin and glucose concentrations were log transformed. All models were adjusted for history of coronary heart disease (CHD) and continuous values of age, number of years smoked, number of cigarettes smoked daily, and BMI. Models with nutrient covariates additionally included total calories.

BMI was calculated as weight in kilograms divided by height in meters squared. We categorized physical activity according to four levels of occupational activity (not currently working, mostly sitting, walking but no lifting, and lifting frequently) and three levels of leisure-time activity (mostly sedentary, moderate, or vigorous activity). CHD was defined as self-reported history of angina and/or myocardial infarction. With the exception of alcohol, which is not highly correlated with energy intake (Spearman's $\rho = 0.13$), nutrients were energy adjusted using the residual method (27). Dietary available carbohydrate intake, which

includes dietary starch and sugar, was calculated as total carbohydrate minus fiber intake to differentiate carbohydrates from food that are available for digestion and absorption from non-digestible components, such as fiber.

Proportional hazards models—Only cohort participants with complete relevant baseline information ($n=27,035$) were included in the prospective analysis. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% CIs adjusted for potential confounding variables. Continuous exposure variables of interest were modeled continuously and in quintiles. We also created BMI categories for underweight, normal weight, overweight, obese, and severely obese using World Health Organization cut-points of <18.5 , $18.5\text{--}24.9$, $25\text{--}29.9$, $30\text{--}34.9$, and ≥ 35 kg/m², respectively (28).

We included age at randomization, BMI, number of cigarettes smoked daily, and number of years smoked in multivariable models (all modeled continuously), as all are considered putative risk factors for pancreatic cancer, though only age at randomization and number of years smoked were significantly associated with pancreatic cancer. Models with nutrient covariates were additionally adjusted for total calories. We included self-reported history of diabetes mellitus as a variable in separate models because dietary and lifestyle factors may both cause (i.e., BMI) and be influenced by (i.e., dietary intake) diabetes status. We considered other potential confounders, such as energy-adjusted intakes of saturated fat, total fat, carbohydrate, or folate, self-reported history of bronchial asthma, pancreatitis, and occupational or leisure-time physical activity, but inclusion of these factors immaterially changed our risk estimates.

We tested the assumption that hazards were proportional over time using graphical methods, as well as the likelihood ratio test comparing models with an interaction term for each covariate of interest by follow-up time to models without this term. The likelihood ratio test was used to test effect modification on the multiplicative scale by BMI, age at randomization, self-reported diabetes history, and number of cigarettes smoked daily by comparing models with and without cross-product terms. Results were also obtained after exclusion of self-reported diabetics. All statistical analyses were conducted using Stata software version 9.0 (Statacorp, College Station, TX).

RESULTS

The randomly sampled subcohort of participants with fasting measurements of insulin and glucose were similar to all ATBC Study cohort participants with respect to medians and distributions of general, clinical, dietary, and smoking variables (Table 1).

The final linear regression models for predictors of fasting serum insulin and glucose among non-diabetics in the ATBC subcohort are shown in Table 2. In multivariable adjusted models, we observed significant positive associations for BMI (per 5 kg/m², $\beta=0.41$, 95% CI 0.35, 0.48) and energy-adjusted intakes of total fat (per 10 g/d, $\beta=0.03$, 95% CI 0.003, 0.06) and saturated fat (per 10 g/d, $\beta=0.04$, 95% CI 0.003, 0.07) with fasting insulin concentrations, while serum HDL-cholesterol (per 0.5 mmol/L, $\beta=-0.13$, 95% CI -0.22 , -0.05) and alcohol intake (per 10 g/d, $\beta=-0.03$, 95% CI -0.05 , -0.006) were inversely associated with insulin. Height, blood pressure, physical activity, and energy-adjusted intakes of available carbohydrates, sucrose, starch, fiber, and protein were not associated with fasting insulin concentrations.

BMI (per 5 kg/m², $\beta=0.03$, 95% CI 0.01, 0.05) was positively associated while and energy-adjusted intakes of available carbohydrates (per 10 g/d, $\beta=-0.004$, 95% CI -0.007 , -0.0008) and sucrose (per 10 g/d, $\beta=-0.007$, 95% CI -0.01 , -0.002) were inversely associated with fasting glucose concentrations. No associations were observed for serum HDL-cholesterol,

blood pressure, physical activity, alcohol, or energy-adjusted intakes of saturated fat, starch, fiber, or protein.

Smoking habits (number of cigarettes smoked daily or number of years smoked) did not modify any of the above associations (p -interaction>0.05).

Table 3 presents the hazards ratios for pancreatic cancer according to factors that were statistically significantly associated with either fasting insulin or glucose concentrations. All risk estimates were proportional over time. Greater intake of energy-adjusted saturated fat was associated with a non-significant increased risk of pancreatic cancer (highest vs lowest quintile, HR=1.38, 95% CI 0.97, 1.98, p -trend=0.06). A significant increased risk of pancreatic cancer was observed with greater energy-adjusted total fat intake (highest vs lowest quintile, HR=1.54, 95% CI 1.05, 2.25, p -trend=0.01). Greater intake of energy-adjusted available carbohydrates (highest vs lowest quintile, HR= 0.63, 95% CI 0.44, 0.90, p -trend=0.01) and sucrose (highest vs lowest quintile, HR=0.62, 95% CI 0.43, 0.89, p -trend=0.09) were associated with reduced risk of pancreatic cancer. Because the first quintile of energy-adjusted sucrose intake included a higher proportion of self-reported diabetics (13.0% vs 0.7% in the fifth quintile), the inverse trend association was slightly attenuated after adjustment for self-reported diabetes (highest vs. lowest quintile, HR=0.68, 95% CI 0.47, 0.98, p -trend=0.25) and after excluding self-reported diabetics (highest vs. lowest quintile, HR=0.63, 95% CI 0.43, 0.92, p -trend=0.20). Within strata of BMI, the inverse association for energy-adjusted sucrose intake was stronger among normal-weight (BMI <25 kg/m²) (highest vs. lowest quintile, HR= 0.46, 95% CI 0.24, 0.88, p -trend=0.01) compared to overweight (BMI ≥25 kg/m²) (highest vs. lowest quintile, HR= 0.76, 95% CI 0.49, 1.18, p -trend=0.41) participants, but the test for interaction was not statistically significant (p -interaction=0.08). No significant associations were observed according to increasing quintiles or continuous values of BMI (data not shown), serum HDL-cholesterol, height, or alcohol intake.

When we categorized BMI according to normal-weight, overweight, obese, and severely obese, the relative risks were 1.00, 0.99, 1.08, and 1.55, respectively (Table 3). Because only 8 cases were severely obese, the confidence intervals were wide. Number of cigarettes smoked daily (<20, 20, and ≥20 cigarettes; p -interaction= 0.89) or number of years smoked (<34 years, 34–40, ≥41 years; p -interaction= 0.32) did not modify the relation between BMI and pancreatic cancer risk.

We also calculated the risk estimates for factors that were not statistically significantly associated with fasting insulin or glucose concentrations from Table 2, such as blood pressure, leisure-time physical activity, and energy-adjusted intakes of fiber, starch, and protein and did not observe significant associations (data not shown). However, compared to sedentary, moderate/heavy occupational physical activity was associated with a statistically significant reduced risk of pancreatic cancer (HR=0.64, 95% CI 0.44, 0.93). These findings are in agreement with previous ATBC studies that had seven fewer years of follow-up time and half as many pancreatic cancer cases (21–22).

When the first five years of follow-up were excluded, changes in the risk estimates for all exposures were negligible overall after adjusting for age, BMI, and smoking. However, the positive trend association for energy-adjusted saturated fat intake was attenuated despite a stronger hazard ratio in the highest compared to lowest quintile of intake (n =238 cases, HR=1.49, 95% CI 0.98, 2.24, p -trend=0.13).

DISCUSSION

We extended our previous study (10) in the ATBC study by examining whether potentially modifiable lifestyle factors associated with concentrations of fasting insulin and glucose were

also associated with pancreatic cancer risk. We found that greater dietary fat intake, specifically saturated fat, was positively associated with both fasting insulin concentrations and pancreatic cancer risk. Greater dietary intakes of available carbohydrates and sucrose were associated with lower fasting glucose concentrations and reduced pancreatic cancer risk, although the association showed a threshold pattern with sucrose intake greater than the first quintile. Other factors, such as BMI, height, serum HDL-cholesterol, and alcohol intake, were not significantly associated with risk of pancreatic cancer, despite strong positive associations for these factors with fasting insulin or glucose concentrations in the subcohort. These results suggest that diet may partially explain the positive association between fasting insulin concentrations and pancreatic cancer risk that was observed previously in the ATBC Study (10).

Consistent evidence supports an association between dietary saturated fat intake and reduced insulin sensitivity or greater fasting/postprandial insulin levels independent of body fat. Most of the evidence on this topic derives from observational studies (16–18). A large randomized controlled feeding study of 162 healthy participants, the KANWU study (named after participating centers Kuopio, Aarhus, Naples, Wollongong, Uppsala), found that after three months a high saturated fat diet (17% of total energy) reduced insulin sensitivity by 10%, whereas a high monounsaturated diet had no effect (29). Saturated fats may alter the fatty acid composition of the cell membranes, thereby reducing insulin receptor binding or affinity and altering ion permeability and insulin signaling (30). Of twelve case-control studies that have examined fat intake and pancreatic cancer (31–42), six studies (34–39) found associations between saturated fat intake and pancreatic cancer that were either null or mixed (i.e., different according to gender). Three case-control studies observed a greater risk with higher saturated fat intake (31–33), though in one of these studies 75% of the 179 cases were proxy respondents (31). Apart from the ATBC Study, no other prospective investigation has shown an increased risk of pancreatic cancer with greater saturated fat intake (43–44). The inconsistencies in results for dietary fat intakes and pancreatic cancer risk across populations may be explained by differences in trends in saturated fat intake over time and common sources of dietary fat. Some studies included a small number of pancreatic cancer cases and/or a narrow range of saturated fat intake and therefore had limited ability to observe associations if they existed. For instance, in the ATBC Study, median values of the lowest and highest quintile of saturated fat intake were 36 and 69 grams per day, respectively, while these values in the Nurses' Health Study were 20 and 36 grams per day (43). Epidemiologic evidence is lacking on whether smoking modifies the association between saturated fat intake and pancreatic cancer, though in this study of current smokers the association between saturated fat and pancreatic cancer was not modified by smoking dose or duration.

Overall evidence from case-control and prospective studies does not support an association between dietary carbohydrates, glycemic load, and pancreatic cancer risk (34,45–50), though positive (31,51) and mixed (i.e., different according to gender or exposure definition) (33,35, 52) associations have also been observed. The statistically significant increased risk in the highest compared to lowest quartile of dietary glycemic load among participants in the Nurses' Health Study, who were both overweight and sedentary (HR=2.67, 95% CI 1.02, 6.99) (45), was not confirmed in five subsequent prospective studies (46–50). In the Canadian National Breast Screening Study and the Netherlands Cohort Study, statistically significant or non-significant inverse associations for dietary glycemic load, total carbohydrates, and mono- and disaccharides with pancreatic cancer risk were observed in minimally-adjusted models but not in multivariable-adjusted models (46,50). In the latter study, the risk estimates may have been attenuated due to the adjustment for fruit, vegetable, and fiber intakes, all of which contribute to total carbohydrate intake (50). The inverse associations we observed for available carbohydrate and sucrose intakes with pancreatic cancer risk are consistent with the previous ATBC study result with follow-up through 1997 (22). In the ATBC subcohort, we also observed linear inverse associations for intakes of these nutrients with fasting glucose

concentrations, which were positively associated with pancreatic cancer risk in a previous case-cohort analysis in the ATBC Study (10). In relation to pancreatic cancer risk, the inverse trend associations were slightly attenuated after excluding self-reported diabetics, who comprised a higher proportion of the low-intake reference group. The ATBC Study differs from other prospective cohorts in terms of smoking, so our results may not be generalizable to other populations. Residual confounding by a correlate of available carbohydrate or sucrose intake may also explain the inverse associations with pancreatic cancer risk. Additionally, we cannot rule out chance as an explanation for these findings, given the overall lack of support from analyses conducted in other cohorts.

BMI and serum HDL-cholesterol were strongly associated with fasting serum insulin concentrations, but neither factor was associated with risk for pancreatic cancer in our study. It is possible that the relationship between BMI and pancreatic cancer risk may be masked in current or ever smokers (21,53). Elevated serum cholesterol and blood pressure are correlated with insulin resistance, but these conditions have not been significantly associated with risk of pancreatic cancer in epidemiologic studies (21,54–55). The Korean Cancer Prevention Study, which previously showed a positive association between fasting glucose concentrations and pancreatic cancer risk (8), found no associations for BMI, blood pressure, and serum cholesterol despite strong positive associations with fasting serum glucose concentrations (55).

Strengths of the ATBC Study include the prospective design, extensive follow-up, biomarker and anthropometric measurements, relatively valid and reliable dietary information, and baseline information on potential confounders. The Finnish Cancer Registry has nearly complete cancer ascertainment in Finland (25). The confirmation of pancreatic cancer cases by review of medical records during early follow-up is a strength (25,56). After an additional seven years of follow-up, our results confirm those from previous analyses in the ATBC Study that dietary, anthropometric, behavioral, and clinical factors in relation to pancreatic cancer risk and found positive associations for number of cigarettes smoked daily (23), higher dietary intakes of total and saturated fat (22), and self-reported history of type 2 diabetes (21), and inverse associations for greater overall physical activity (21) and higher dietary intakes of sucrose and total carbohydrates (22). The consistency between the earlier and present study and the fact that the hazard ratios were proportional over time provides evidence against reverse causation or misclassification over the long period of follow-up. Prospective follow-up in the current study precludes bias due to selection of participants, survival, differential recall of past exposures between cases and controls, and proxy reporting, as well as ambiguous timing between exposure and pancreatic cancer diagnosis.

Some limitations should be noted. We lacked information on waist circumference, serum triglycerides, and medication use all which could be associated with fasting serum insulin or glucose concentrations in the ATBC subcohort. Fasting insulin and glucose concentrations were measured only once, which would not account for variability in these serum markers over time. We may have underestimated baseline diabetes prevalence in the larger cohort because we relied on self-report. In addition, the clinical definition for diabetes has changed since the ATBC study was initiated. For example, the clinical definition for diabetes was fasting glucose concentrations of ≥ 140 mg/dl in the 1980s, but the cut-off was lowered to ≥ 126 mg/dl in 1995 (57). Because all participants were current smokers at baseline, we were concerned that residual confounding from cigarette smoking may have attenuated our relative risk estimates; however, smoking adjustment and restriction to participants who smoked 20 cigarettes per day did not change our results. Finally, results from this study may not be generalizable to other populations, particularly non-smokers and women. Nonetheless, many associations observed in the ATBC Study are consistent with that of other prospective cohorts, including associations for folate (58), type 2 diabetes (7), and fasting glucose concentrations (8,11).

In conclusion, we found that dietary total and saturated fat are associated with higher fasting insulin concentrations and may increase the risk of pancreatic cancer. However, this study does not provide evidence that other factors related to fasting insulin or glucose concentrations, such as BMI, height, HDL-cholesterol, or alcohol intake, increase the risk of pancreatic cancer in smokers.

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Table 1

General, anthropometric, clinical, and dietary characteristics of participants at baseline (1985–88) in the subcohort and cohort

Characteristic	Subcohort	Cohort
	Median (IQR) or percentage	Median (IQR) or percentage
Number of participants	366	27,035
Age (years)	56 (52–60)	57 (53–61)
Pack years of smoking	34 (24–45)	35 (24–46)
Number of cigarettes smoked daily	20 (15–25)	20 (15–25)
Number of years smoked	35 (30–40)	36 (31–42)
Body mass index (kg/m ²)	26.1 (23.8–28.5)	26.0 (23.7–28.5)
Systolic blood pressure (mmHg)	140 (128–152)	140 (128–154)
Diastolic blood pressure (mmHg)	88 (80–94)	88 (80–94)
Serum cholesterol (mmol/L)	6.25 (5.51–7.13)	6.16 (5.45–6.95)
Serum high-density lipoprotein (mmol/L)	1.16 (0.99–1.37)	1.14 (0.97–1.36)
Fasting serum insulin (μIU/mL)	4.1 (2.7–5.8)	N/A
Fasting serum glucose (mg/dL)	98 (92–106)	N/A
Diabetes (self-report)	0	4.2%
Diabetes (clinical: glucose ≥ 126 mg/dL)	2.5%	N/A
Total energy (kcal)	2,608 (2,207–3,156)	2,600 (2,156–3,120)
Fatty acids (g) [†]	101.5 (92.4–110.3)	101.2 (92.1–110.1)
Saturated fatty acids (g) [†]	52.6 (44.5–60.7)	52.3 (43.9–61.0)
Available carbohydrates (g) [†]	267.4 (242.8–293.5)	266.2 (243.0–289.4)
Fiber (g) [†]	17.6 (13.2–23.7)	18.0 (12.8–23.8)
Sucrose (g) [†]	51.6 (37.4–65.8)	51.1 (37.4–66.8)
Protein (g) [†]	95.1 (86.3–101.4)	94.4 (87.0–102.2)
Alcohol (g)	11.4 (2.2–26.9)	11.0 (2.56–25.6)

[†]Energy adjusted using the residual method

Table 2
Final linear regression of fasting serum insulin ($\mu\text{IU/mL}$) and glucose (mg/dL), excluding self-reported diabetics ($n=366$)

	Log _e insulin ($\mu\text{IU/mL}$)			Log _e glucose (mg/dL)		
	$\beta^{\dagger}$	95% CI	<i>p</i>	$\beta^{\dagger}$	95% CI	<i>p</i>
Body mass index (measured: per 5 kg/m^2)	0.41	0.35, 0.48	<0.001	0.03	0.01, 0.05	<0.001
Height (per 5 cm)	0.03	-0.007, 0.07	0.11	0.01	0.002, 0.02	0.02
High-density lipoprotein (measured: per 0.5 mmol/L)	-0.13	-0.22, -0.05	0.002	0.02	-0.002, 0.04	0.08
Diastolic blood pressure (measured: per 10 mmHg)	0.04	-0.01, 0.08	0.11	0.002	-0.009, 0.01	0.67
Systolic blood pressure (measured: per 10 mmHg)	0.02	-0.01, 0.04	0.18	0.005	-0.002, 0.01	0.15
Total fat (per 10 g) $\dagger\ddagger$	0.03	0.003, 0.06	0.03	0.007	-0.00008, 0.02	0.05
Saturated fat (per 10 g) $\dagger\ddagger$	0.04	0.003, 0.07	0.04	0.002	-0.007, 0.01	0.61
Available carbohydrates (per 10 g) $\dagger\ddagger$	-0.0006	-0.013, 0.01	0.92	-0.004	-0.007, -0.0008	0.01
Sucrose (per 10 g) $\dagger\ddagger$	0.01	-0.01, 0.03	0.35	-0.007	-0.01, -0.002	0.01
Starch (per 10 g) $\dagger\ddagger$	-0.01	-0.02, 0.01	0.39	-0.002	-0.005, 0.002	0.36
Fiber (per 10 g) $\dagger\ddagger$	-0.03	-0.09, 0.03	0.29	-0.006	-0.02, 0.009	0.44
Protein (per 10 g) $\dagger\ddagger$	0.02	-0.02, 0.06	0.40	0.008	-0.002, 0.02	0.10
Alcohol (per 10 g)	-0.03	-0.05, -0.006	0.01	-0.00008	-0.005, 0.005	0.98
Physical activity at work						
Sedentary	Ref	0		Ref	0	
Moderate	-0.11	-0.28, 0.07	0.24	0.04	-0.01, 0.08	0.11
Heavy	-0.14	-0.31, 0.02	0.09	0.04	-0.004, 0.08	0.08
Not working	-0.02	-0.19, 0.15	0.85	0.02	-0.02, 0.07	0.27
			0.18 $\ddagger$			0.30 $\ddagger$
Physical activity in leisure						
Sedentary	Ref	0		Ref	0	
Moderate	-0.0001	-0.10, 0.10	0.99	0.001	-0.02, 0.03	0.92
Heavy	-0.21	-0.43, 0.01	0.06	-0.01	-0.07, 0.04	0.60
			0.14 $\ddagger$			0.85 $\ddagger$

$\dagger$ Adjusted for age (per 5 years), body mass index (per 5 kg/m^2), coronary heart disease (self-reported), number of cigarettes per day (per cigarette), and years smoked (per year)

$\ddagger$ Adjusted for age (per 5 years), body mass index (per 5 kg/m^2), coronary heart disease (self-reported), number of cigarettes per day (per cigarette), and years smoked (per year), and total calories (per 500 kcal/day)

[§]Energy adjusted using the residual method
[¶]P-value from test that all dummy coefficients are equal to zero

Table 3
Hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer by factors associated with fasting insulin and/or glucose (n=27,035)

Variable	Quintile					Continuous [#]	p-trend
	1	2	3	4	5		
Body mass index (kg/m ²)	23.1 (<25)	27.0 (25–29.9)	31.5 (30–34.9)	36.9 (≥35)			
No. cases	117	139	41	8			
Adjusted [†]	1.00 (ref)	0.99 (0.77, 1.26)	1.08 (0.75, 1.54)	1.55 (0.76, 3.19)		1.02 (0.95, 1.09)	0.54
Adjusted [‡]	1.00 (ref)	0.97 (0.76, 1.24)	1.03 (0.72, 1.47)	1.42 (0.69, 2.93)		1.01 (0.94, 1.08)	0.80
Height (cm)	167 (<170)**	171 (170–172)	174 (173–175)	177 (176–179)	182 (≥180)		
No. cases	74	56	56	61	58		
Adjusted [†]	1.00 (ref)	1.05 (0.74, 1.48)	1.01 (0.72, 1.44)	1.01 (0.72, 1.43)	1.25 (0.88, 1.77)	1.03 (0.97, 1.09)	0.39
Adjusted [‡]	1.00 (ref)	1.05 (0.74, 1.48)	1.01 (0.71, 1.43)	1.01 (0.72, 1.42)	1.23 (0.87, 1.75)	1.03 (0.96, 1.09)	0.43
Serum high-density lipoprotein (mmol/L)	0.84 (<0.93)	1.01 (0.93–1.07)	1.15 (1.07–1.22)	1.31 (1.22–1.43)	1.61 (≥1.43)		
No. cases	66	49	76	49	65		
Adjusted [†]	1.00 (ref)	0.71 (0.49, 1.02)	1.11 (0.79, 1.55)	0.72 (0.49, 1.05)	1.00 (0.70, 1.43)	1.00 (0.96, 1.05)	0.95
Adjusted [‡]	1.00 (ref)	0.72 (0.50, 1.05)	1.15 (0.82, 1.61)	0.75 (0.51, 1.09)	1.04 (0.72, 1.50)	1.01 (0.96, 1.05)	0.80
Total fat (g/d) [§]	82.9 (<89.7)	94.2 (89.7–97.9)	101.2 (97.9–104.5)	108.1 (104.5–112.5)	119.2 (≥112.5)		
No. cases	43	79	46	67	70		
Adjusted [†]	1.00 (ref)	1.72 (1.18, 2.50)	1.00 (0.65, 1.52)	1.45 (0.99, 2.14)	1.54 (1.05, 2.25)	1.08 (1.02, 1.14)	0.01
Adjusted [‡]	1.00 (ref)	1.72 (1.18, 2.50)	1.00 (0.65, 1.52)	1.45 (0.98, 2.13)	1.52 (1.04, 2.22)	1.07 (1.01, 1.14)	0.01
Saturated fat (g/d) [§]	36.3 (<41.9)	45.7 (41.9–49.1)	52.3 (49.1–55.5)	59.0 (55.5–63.2)	69.2 (≥63.2)		
No. cases	51	49	65	64	76		
Adjusted [†]	1.00 (ref)	0.90 (0.60, 1.33)	1.17 (0.81, 1.70)	1.16 (0.80, 1.69)	1.38 (0.97, 1.98)	1.06 (1.00, 1.13)	0.06
Adjusted [‡]	1.00 (ref)	0.90 (0.61, 1.35)	1.19 (0.82, 1.73)	1.19 (0.82, 1.72)	1.40 (0.98, 2.01)	1.06 (1.00, 1.13)	0.05
Available carbohydrates (g/d) [§]	221 (<237)	248 (237–257)	266 (257–275)	284 (275–295)	312 (≥295)		
No. cases	78	56	59	58	54		
Adjusted [†]	1.00 (ref)	0.66 (0.47, 0.94)	0.69 (0.49, 0.97)	0.65 (0.46, 0.92)	0.63 (0.44, 0.90)	0.92 (0.87, 0.98)	0.01
Adjusted [‡]	1.00 (ref)	0.67 (0.48, 0.95)	0.70 (0.50, 0.99)	0.67 (0.47, 0.95)	0.65 (0.46, 0.93)	0.93 (0.88, 0.99)	0.02
Sucrose (g/d) [§]	24.9 (<33.8)	40.4 (33.8–45.8)	51.1 (45.8–56.8)	63.2 (56.8–71.3)	84.3 (≥71.3)		
No. cases	75	57	63	59	51		

Variable	Quintile					Continuous [#]	p-trend
	1	2	3	4	5		
Adjusted [†]	1.00 (ref)	0.69 (0.49, 0.98)	0.76 (0.54, 1.07)	0.70 (0.50, 1.00)	0.62 (0.43, 0.89)	0.95 (0.89, 1.01)	0.09
Adjusted [‡]	1.00 (ref)	0.74 (0.52, 1.06)	0.83 (0.58, 1.18)	0.77 (0.54, 1.10)	0.68 (0.47, 0.98)	0.97 (0.91, 1.03)	0.25
Alcohol (g/d)	0 (<1.6)	4.1 (1.6–7.1)	11.1 (7.1–16.0)	22.9 (16.0–29.5)	44.8 (≥29.5)		
No. cases	65	67	58	49	66		
Adjusted [†]	1.00 (ref)	1.03 (0.73, 1.45)	0.92 (0.64, 1.31)	0.81 (0.56, 1.18)	1.16 (0.82, 1.65)	1.01 (0.96, 1.07)	0.58
Adjusted [‡]	1.00 (ref)	1.04 (0.74, 1.46)	0.92 (0.65, 1.32)	0.82 (0.57, 1.20)	1.17 (0.82, 1.66)	1.02 (0.97, 1.07)	0.56

[†] Adjusted for age, BMI, number of cigarettes per day, and years of smoking

[‡] Adjusted for age, BMI, number of cigarettes per day, years of smoking, and total calories (per 500 kcal/day)

[§] Energy adjusted using the residual method

^{||} Additionally adjusted for self-reported diabetes mellitus

[#] Continuous HRs were standardized to the average size of the 3 central quintiles (top minus bottom quintile cutpoints divided by 3) and represent an average change in 20% of the distribution in the cohort

*** Median (range)