

Association between Pancreatic Fat and Incidence of Metabolic Syndrome: A 5-Year Japanese Cohort Study

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Disclosure: This study received no financial support relevant to this work. All authors have no potential conflicts of interest associated with this study.

Acknowledgements

The authors appreciate Keita Numata from the System Development Section, Keijinkai Maruyama Clinic; Kunihiko Hayashi, Hiromitsu Yonezawa, Eiji Kazuta, Kimihiro Saito, Keiko Takasaki, and Miyuki Yoshioka from the Department of Radiology, Keijinkai Maruyama Clinic; and Yuki Yoshino from the Department of Radiology, Teine Keijinkai Hospital for assistance in data collection. We would also like to thank Editage (www.editage.jp) for English language editing.

Author contributions: *H.Y., M.K., Y.Y., S.Fukuma* designed the study. *S.T., M.D., N.H., and Y.K.* collected the data. *H.Y.* drafted the manuscript and analyzed the data. *H.Y., S.T., M.K., M.D., N.H., Y.K., A.K., Y.Y., S.Fukuma, and S.Fukuhara* reviewed, made critical revisions, and approved the article before submission. *S. Fukuhara* is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Association between Pancreatic Fat and Incidence of Metabolic Syndrome: A 5-Year Japanese Cohort Study

Abstract

Background and Aim: Previous cross-sectional studies showed that pancreatic fat was associated with metabolic syndrome. However, no longitudinal study has evaluated whether people with high pancreatic fat are likely to develop future metabolic syndrome. We investigated the association between baseline pancreatic fat and metabolic syndrome incidence.

Methods: In 2008–2009, 320 participants without metabolic syndrome underwent health checks, which included unenhanced computed tomography (CT), and were followed up annually for 4–5 years. Baseline pancreatic fat amounts were evaluated using a histologically validated method that measured differences between pancreas and spleen attenuations (P-S) on CT. The participants were divided into low (reference), intermediate, and high pancreatic fat groups based on P-S tertiles. Metabolic syndrome incidence was evaluated annually over a median follow-up period of 4.99 (interquartile range, 4.88–5.05) years, in accordance with the 2009 harmonized criteria. Risk ratios (RRs) for the association between baseline pancreatic fat amounts and metabolic syndrome incidence were estimated using Poisson regression models adjusted for age, sex, BMI, liver fat, pre-metabolic syndrome, cigarette use, alcohol use, and physical activity.

Results: Metabolic syndrome incidence was 30.6% (98/320). Pancreatic fat was associated with an increased incidence of metabolic syndrome, based on a univariate analysis (RRs [95% CI], 3.14 [1.74–5.67] and 3.96 [2.23–7.03] in the intermediate and high pancreatic fat groups, respectively). The association remained statistically significant in the multivariate analysis (RR [95% CI], 2.04 [1.14–3.64] and 2.30 [1.28–4.14] for the same groups, respectively).

Conclusions: Pancreatic fat predicts the future risk of metabolic syndrome.

Keywords: fat; pancreas; metabolic syndrome; cohort; longitudinal

Introduction

Worldwide, metabolic syndrome is increasing and has become a major public health problem¹⁻³ because it increases the risk of developing type 2 diabetes, cardiovascular disease, chronic kidney disease, cancer, and mortality⁴⁻⁷. Visceral fat, rather than subcutaneous fat, is considered to have a central role in the development of metabolic syndrome^{8,9}. In addition to subcutaneous and visceral fat, ectopic fat has also been vigorously researched during the past decade. Ectopic fat is fat that has accumulated in organs, such as the liver and pancreas, which normally contain little fat¹⁰. Many studies have shown that liver fat is a risk factor of both metabolic and liver diseases such as metabolic syndrome, type 2 diabetes, nonalcoholic steatohepatitis, and liver cancer¹¹⁻¹⁴. Unlike in the case of liver fat, the predictive role of pancreatic fat on metabolic and pancreatic diseases is unknown.

Clinical practice guidelines recommend abdominal ultrasonography for patients with metabolic risk factors or abnormal liver chemistries^{14,15}. Pancreatic fat can be detected using routine abdominal ultrasonography more frequently than can liver fat¹⁶, and it was reported that the prevalence of fatty pancreas was 16%¹⁷. A previous study used magnetic resonance imaging to show that 16.1% of the general population had more than 10% fat in the pancreas and that half of these individuals were not obese¹⁸. Although pancreatic and visceral fat amounts did not correlate with each other in a histological study¹⁹, several cross-sectional studies showed a significant association between pancreatic fat amounts and the presence of metabolic syndrome²⁰⁻²². Pancreatic fat is, therefore, speculated to be an early manifestation of metabolic syndrome independently of central obesity. However, longitudinal studies that have evaluated whether people with high pancreatic fat are likely to develop future metabolic syndrome have not been published.

This 5-year cohort study investigated the association between pancreatic fat amounts at baseline and the incidence of metabolic syndrome during follow-up.

Methods

Participants

This retrospective cohort study was conducted using unenhanced computed tomography (CT) images obtained during routine health checks at Keijinkai Maruyama Clinic, Sapporo, Japan. Health checks involving imaging modalities, such as CT, are common in Japan, and many Japanese people are willing to undergo health checks at their own expense every year. In fact, the Japanese imaging guideline reported that the number of CT systems is the highest among 27 countries: 97.4 CT systems per one million people in Japan versus 21.1 CT systems per one million people on average for various countries. Given this high accessibility to CT, the annual number of CT examinations is 146.1 in 1000 people in Japan²³. This study was conducted based on the secondary use of the health check data at Keijinkai Maruyama Clinic^{24, 25}. A total of 1053 participants underwent a health check involving baseline CT (between April 1, 2008 and March 31, 2009), with 779 participants selected after excluding participants with metabolic syndrome ($n = 258$), missing data ($n = 10$), pancreatic atrophy ($n = 3$), previous pancreatic resection ($n = 1$), previous splenic resection ($n = 1$), and ambiguous pancreatic margins ($n = 1$). No other pancreatic abnormality, such as calcification, was found. An experienced radiologist, blinded to participant information, excluded the participants based on the CT images. Of the 779 participants, 664 underwent varying numbers of health checks over the subsequent <6 years (referred to as “any follow-up” participants). Of these 664 individuals, the 320 participants who underwent annual follow-ups during the following 4–5 years (“annual follow-up” participants) were included in the primary analysis. The median follow-up period was 4.99 (interquartile range [IQR], 4.88–5.05) years (**Figure 1**).

Pancreatic Fat

Pancreatic fat amounts were evaluated using a histologically validated method that involved measuring the difference between the mean pancreas and spleen attenuations (P-S) on

unenhanced CT. Round regions of interest (ROIs), with areas of 1.0 cm², were placed on the pancreatic head, body, and tail to calculate the mean pancreatic attenuation. The mean splenic attenuation was estimated by placing three similar ROIs on the largest spleen slices. A previous validation study reported a Spearman correlation coefficient, between P-S values and histologic pancreatic fat amounts, of -0.62. Moreover, no significant correlation between pancreatic and visceral fat amounts was shown in the validation study (Spearman correlation coefficient, -0.009 (p = 0.94))¹⁹. We used -(P-S) as an indicator of pancreatic fat.

Unenhanced CT was performed using a single-slice helical scanner (Asteion KG TSX-021B; Toshiba, Otawara, Japan). The scanner settings were: 120 kVp, 170 mAs, 10-mm collimation, 10-mm slice thickness, pitch of 1.0, and a 10-mm reconstruction interval. Seven experienced radiologic technologists measured pancreatic and splenic attenuations on a CT workstation (TWS-5000, Toshiba) under the supervision of an experienced radiologist. All the radiologic technologists and radiologists were blinded to the detailed participant information.

The participants were divided into low, intermediate, and high pancreatic fat groups based on -(P-S) tertiles because there is no apparent cut-off for pancreatic fat amounts. The low pancreatic fat group was considered the reference group because the pancreas normally contains little fat¹⁰.

Metabolic Syndrome

Metabolic syndrome was diagnosed using the 2009 harmonized criteria established by organizations including the International Diabetes Federation, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity. Participants were diagnosed with metabolic syndrome if they met any three or more of the following criteria: central obesity (waist circumference ≥ 90 cm [men] or ≥ 80 cm [women]), elevated blood pressure (≥ 130 mmHg systolic, ≥ 85 mmHg diastolic, or antihypertensive drug treatment), elevated fasting

plasma glucose levels (≥ 100 mg/dL or antidiabetic drug treatment), elevated triglyceride levels (≥ 150 mg/dL or antidyslipidemic drug treatment), and reduced high-density lipoprotein (HDL) cholesterol levels (< 40 mg/dL [men] or < 50 mg/dL [women] or antidyslipidemic drug treatment)⁴. The incidence of metabolic syndrome was evaluated annually until the participant either developed metabolic syndrome or completed the 4–5-year follow-up.

Medical Evaluation

All participants underwent body measurements and unenhanced CT, and completed questionnaires regarding their medical history, medication use, cigarette smoking, alcohol consumption, and physical activity at baseline. On unenhanced CT images, ROIs with areas of 1.0 cm^2 were placed on the hepatic anterior segment, posterior segment, and left lobe to calculate the mean hepatic attenuation. Liver fat amounts were assessed using a histologically validated method that measured the differences between mean liver and spleen attenuations (L-S) on CT²⁶. We used $-(L-S)$ as an indicator of liver fat. Moreover, we defined participants having only one or two of the metabolic syndrome criteria as being pre-metabolic syndrome-1 or pre-metabolic syndrome-2, respectively. Both the amounts and frequencies of alcohol consumption were assessed; ethanol intake ≥ 20 g/day was considered significant²⁷. The participants were regarded as “physically active” if they had been physically active for ≥ 30 min, ≥ 2 times a week, over a period of ≥ 1 year.

Statistical Analysis

Baseline characteristics are expressed as means (standard deviation [SD]). Poisson regression models with robust variance were used to estimate risk ratios (RRs) and 95% CIs for associations between baseline pancreatic fat amounts and the incidence of metabolic syndrome. The incidences of metabolic syndrome in the intermediate and high pancreatic fat groups were compared with that in the low pancreatic fat group. The multivariate analysis was adjusted for

age, sex, BMI, liver fat, pre-metabolic syndrome-1, pre-metabolic syndrome-2, current smoking status, ethanol intake ≥ 20 g/day, and physical activity. These potential confounders were selected based on previous studies without using any statistical selection methods^{18, 20, 22, 28, 29}. This primary analysis was conducted using the data for the 320 annual follow-up participants. We selected Poisson regression models, instead of logistic regression models, because the odds ratios substantially overestimate RRs when the incidence of outcomes is more than 10%³⁰.

For the secondary analysis, we also evaluated each criterion of metabolic syndrome: central obesity, elevated blood pressure, elevated fasting plasma glucose, elevated triglyceride, and reduced HDL cholesterol. For annual follow-up participants who did not meet each criterion of metabolic syndrome at baseline, Poisson regression models with robust variance were used to estimate RRs and 95% CI for the association between baseline pancreatic fat and incidence of meeting each criterion of metabolic syndrome during follow-up. The multivariate analysis was adjusted for age, sex, BMI, liver fat, current smoking, ethanol intake ≥ 20 g/day, and physical activity.

We conducted two sensitivity analyses to confirm the robustness of the primary analysis. First, instead of using categorical data ($-[P-S]$ tertile), we used continuous data ($-[P-S]$ itself) as the pancreatic fat indicator. Second, we considered the possibility of selection bias. Instead of limiting the analysis to the 320 annual follow-up participants, the incidence of metabolic syndrome was evaluated in the 664 “any follow-up” participants at each visit until metabolic syndrome developed or they completed follow-up visits over a period of not more than 6 years.

Moreover, we evaluated interobserver agreement of pancreatic fat ($-[P-S]$) and liver fat ($-[L-S]$) measurements on CT in 50 randomly selected participants at baseline. In addition to the radiologic technologists being under the supervision of an experienced radiologist, an independent radiologist evaluated both $-(P-S)$ and $-(L-S)$ in the same 50 participants, as previously described^{24, 25}. We estimated intraclass correlation coefficients between the data

from the radiologic technologists and the independent radiologist using a two-way random-effects model.

A P-value < 0.05 was considered statistically significant. Stata 14 (StataCorp, College Station, TX, USA) was used to complete the statistical analyses.

Ethical Considerations

This study was approved by the ethics committee of Kyoto University, Teine Keijinkai Hospital, and Keijinkai Maruyama Clinic.

Results

Baseline Characteristics

Table 1 shows the baseline data for the study participants. Pancreatic fat (–[P–S]) values were 3.2 (SD 2.3), 8.9 (SD 1.6), and 19.7 (SD 9.5) HU in the low, intermediate, and high pancreatic fat groups, respectively. As age, BMI, liver fat, and prevalence of pre-metabolic syndrome increased, the amount of pancreatic fat also increased.

Association between Pancreatic Fat and Incidence of Metabolic Syndrome (Primary Analysis)

The overall incidence of metabolic syndrome was 30.6% (98/320) during the median follow-up period of 4.99 (IQR, 4.88–5.05) years. The incidence of metabolic syndrome increased in conjunction with the baseline amount of pancreatic fat: 11.3% (12/106), 35.5% (38/107), and 44.9% (48/107) in the low, intermediate, and high pancreatic fat groups, respectively. **Table 2** shows the RRs and 95% CIs for the association between baseline pancreatic fat amounts and the incidence of metabolic syndrome during follow-up. In the univariate analysis, pancreatic fat was significantly associated with an increased incidence of metabolic syndrome. The crude RRs were 3.14 (95% CI 1.74–5.67) and 3.96 (95% CI 2.23–7.03) in the intermediate and high

pancreatic fat groups, respectively. After adjusting for potential confounders, the association remained significant; the adjusted multivariate RRs were 2.04 (95% CI 1.14–3.64) and 2.30 (95% CI 1.28–4.14) in the intermediate and high pancreatic fat groups, respectively.

Association between Pancreatic Fat and Incidence of Meeting Each Criterion of metabolic syndrome (Secondary Analysis)

The incidence of meeting each criterion of metabolic syndrome during follow-up was the followings: central obesity, 24.2% (55/227); elevated blood pressure, 39.3% (84/214); elevated fasting plasma glucose, 30.6% (81/265); elevated triglyceride, 36.5% (101/277); and reduced HDL cholesterol, 19.2% (59/308). **Table 3** shows the RRs and 95% CIs for the association between baseline pancreatic fat amounts and the incidence of meeting each criterion of metabolic syndrome during follow-up. In the multivariate analysis with adjusting potential confounders, the incidence of reduced HDL cholesterol was most strongly associated with baseline pancreatic fat (RRs [95% CI], 2.39 [1.05–5.44] and 3.68 [1.61–8.40] in the intermediate and high pancreatic fat groups, respectively).

Sensitivity Analyses

First, instead of using categorical data (–[P-S] tertile), continuous data (–[P-S] itself) were used to classify pancreatic fat amounts. In the multivariate analysis, every 10 HU increase in pancreatic fat was significantly associated with the incidence of metabolic syndrome, as the adjusted multivariate RR was 1.16 (95% CI, 1.04–1.29). Second, the same analysis as was performed in the primary analysis was repeated using the 664 “any follow-up” participants. The median follow-up period was 4.86 (IQR, 3.36–5.01) years, and the overall incidence of metabolic syndrome was 26.4% (175/664). The adjusted multivariate RRs for the association between pancreatic fat and the incidence of metabolic syndrome were 1.60 (95% CI 1.09–2.35) and 1.73 (95% CI 1.16–2.59) in the intermediate and high pancreatic fat groups, respectively.

The robust association between pancreatic fat amounts and the incidence of metabolic syndrome was confirmed in the two sensitivity analyses.

Interobserver Agreement

Intraclass correlation coefficients between the data from the radiologic technologists and the independent radiologist describing pancreatic fat (–[P-S], 0.91; 95% CI, 0.85–0.95) and liver fat (–[L-S], 0.96; 95% CI, 0.93–0.98) were excellent ³¹.

Discussion

This 5-year cohort study using CT showed that baseline pancreatic fat amounts were independently associated with an increased incidence of metabolic syndrome, after adjusting for potential confounders. The robust association between pancreatic fat amounts and the incidence of metabolic syndrome was confirmed in two sensitivity analyses involving the use of a continuous indicator of pancreatic fat (–[P-S] itself) instead of a categorical indicator of pancreatic fat (–[P-S] tertile) and an analysis involving all participants who underwent follow-up visits (n = 664) instead of using only the annual follow-up participants (n = 320). The present study is the first longitudinal study showing that pancreatic fat is associated with the future risk of metabolic syndrome.

The results of the current study are consistent with those of previous studies. In a systematic review and meta-analysis of 4 cross-sectional studies involving endoscopic ultrasonography, abdominal ultrasonography, or magnetic resonance imaging (n = 2662), pancreatic fat was significantly associated with presence of metabolic syndrome (RR, 2.37; 95% CI, 2.07–2.71) ²⁰. Moreover, a recent cross-sectional study (n = 256) also showed a significant association between pancreatic fat amounts, detected by abdominal ultrasonography, and presence of metabolic syndrome (RR, 4.55; 95% CI, 1.39–14.92) ¹⁶. Our study longitudinally confirmed the association between pancreatic fat and future metabolic syndrome.

Insulin resistance has a central role in the development of metabolic syndrome⁸, and the presence of pancreatic fat is associated with insulin resistance¹⁸. Thus, insulin resistance may result in both pancreatic fat accumulation and metabolic syndrome. Indeed, a recent study longitudinally confirmed the association between prediabetes at baseline and future pancreatic fat accumulation²⁵. Together, these studies and ours suggest that insulin resistance may be a latent predictor for both pancreatic fat and metabolic syndrome, and pancreatic fat accumulation can be detected earlier than can the incidence of metabolic syndrome. Pancreatic fat may be an early manifestation of metabolic syndrome. Both BMI and liver fat, well known risk factors of insulin resistance¹⁰, were not significantly associated with metabolic syndrome in this study, but this might be because of the relatively small sample size. Unfortunately, we do not have data of insulin resistance, and further study with a large sample size is needed to clarify the mechanism.

Patients with metabolic syndrome have a 5-fold increased risk of developing type 2 diabetes⁴. As the present study demonstrated an independent association between pancreatic fat amounts and the incidence of metabolic syndrome, pancreatic fat may also be speculated to be associated with developing type 2 diabetes. A recent systematic review and meta-analysis of 6 cross-sectional studies (n = 10281) found an association between pancreatic fat amounts and the presence of type 2 diabetes (RR, 2.08; 95% CI, 1.44–3.00)²⁰. However, in a previous longitudinal study (n = 813), pancreatic fat was not independently associated with the incidence of type 2 diabetes (hazard ratio, 1.00; 95% CI, 0.98–1.02)²⁴. In fact, incidence of elevated fasting plasma glucose was not associated with baseline pancreatic fat in the present study. Although only the incidence of reduced HDL cholesterol was significantly associated with baseline pancreatic fat among each criterion of metabolic syndrome, this is a secondary analysis with a relatively small sample size to evaluate each criterion of metabolic syndrome. Further large-scale studies need to evaluate longitudinally whether pancreatic fat is associated with the future type 2 diabetes and each criterion of metabolic syndrome.

The present study has three limitations. First, only 41.1% (320/779) of the initial participants underwent annual follow-ups and were included in the primary analysis. This reflects the voluntary nature of the health checks. Considering the possibility of selection bias, we conducted a sensitivity analysis that involved all participants who attended any follow-up health check (85.2% [664/779]) and confirmed the robust association between pancreatic fat and the incidence of metabolic syndrome. Second, we evaluated the amount of pancreatic fat using CT instead of histological examinations because pancreatic biopsies are unethical in healthy participants. However, CT is a histologically validated method, and the interobserver agreement was excellent in our study. Therefore, our method of assessing pancreatic fat appears valid and reliable. Third, the study was conducted in an Asian population. The waist circumference thresholds are different for Asians than for other ethnicities ⁴. Moreover, ethnic differences in the amounts of pancreatic fat have also been reported ³². Further studies in populations of different ethnicities are needed to confirm our results.

In conclusion, this is the first longitudinal study to assess whether people with high pancreatic fat are likely to develop future metabolic syndrome. Our 5-year cohort study showed that baseline pancreatic fat amounts are independently associated with the incidence of metabolic syndrome during follow-up. Thus, pancreatic fat predicts the future risk of metabolic syndrome.

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Table 1. Baseline characteristics of participants

	Low pancreatic fat (n = 106)	Intermediate pancreatic fat (n = 107)	High pancreatic fat (n = 107)
Age (years)	48.9 ± 8.8	52.0 ± 7.9	55.6 ± 9.0
Sex, men/women (n)	82 / 24	96 / 11	96 / 11
BMI (kg/m ²)	22.5 ± 2.5	24.3 ± 3.0	24.6 ± 2.4
Amylase (IU/L)	79.8 ± 23.6	78.0 ± 43.1	67.5 ± 24.7
Pancreatic fat [–(P-S)] (HU)	3.2 ± 2.3	8.9 ± 1.6	19.7 ± 9.5
Liver fat [–(L-S)] (HU)	–10.1 ± 5.2	–6.0 ± 9.2	–5.0 ± 8.3
Pre-metabolic syndrome-1, n (%)	39 (36.8)	32 (29.9)	50 (46.7)
Pre-metabolic syndrome-2, n (%)	15 (14.2)	39 (36.4)	40 (37.4)
Waist circumference (cm)	82.1 ± 7.1	86.5 ± 7.4	87.5 ± 6.4
Systolic blood pressure (mmHg)	116.3 ± 14.0	120.4 ± 14.7	120.7 ± 14.5
Diastolic blood pressure (mmHg)	75.1 ± 9.6	77.3 ± 10.1	77.0 ± 9.1
Antihypertensive drug, n (%)	8 (7.5)	16 (15.0)	19 (17.8)
Fasting plasma glucose (mg/dL)	89.4 ± 11.0	92.8 ± 13.1	97.2 ± 20.0
Antidiabetic drug, n (%)	2 (1.9)	1 (0.93)	3 (2.8)
Triglycerides (mg/dL)	93.5 ± 41.2	108.0 ± 61.6	113.1 ± 72.3
HDL cholesterol (mg/dL)	62.0 ± 14.4	56.8 ± 11.7	57.4 ± 15.1
Antidyslipidemic drug, n (%)	1 (0.94)	1 (0.93)	1 (0.93)
Current smoker	28 (26.4)	30 (28.0)	42 (39.3)
Ethanol intake ≥20 g/day, n (%)	31 (29.2)	39 (36.4)	36 (33.6)
Physical activity, n (%)	34 (32.1)	23 (21.5)	25 (23.4)

Continuous data are expressed as means $\pm$ standard deviation. The participants were divided into low, intermediate, and high pancreatic fat groups, based on $-(P-S)$ tertiles. Missing data: amylase ($n = 16$).

HU, Hounsfield units; P-S, difference between pancreatic and splenic attenuations in unenhanced computed tomography; L-S, difference between liver and spleen attenuations in unenhanced computed tomography; Pre-metabolic syndrome-1, participants who met only one of the metabolic syndrome criteria; Pre-metabolic syndrome-2, participants who met only two of the metabolic syndrome criteria.

Table 2. Risk ratios (RRs) and 95% CIs for the association between baseline pancreatic fat amounts [–(P-S) tertiles] and the incidence of metabolic syndrome

	Annual follow-up participants (n = 320)					
	Crude		Age- and sex-adjusted		Multivariate-adjusted	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Low pancreatic fat	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Intermediate pancreatic fat	3.14 (1.74–5.67)	< 0.001	3.11 (1.68–5.74)	< 0.001	2.04 (1.14–3.64)	0.017
High pancreatic fat	3.96 (2.23–7.03)	< 0.001	3.98 (2.17–7.29)	< 0.001	2.30 (1.28–4.14)	0.005
Age (continuous)			1.00 (0.98–1.01)	0.71	1.00 (0.99–1.02)	0.65
Men			1.18 (0.69–2.00)	0.55	0.91 (0.55–1.51)	0.72
BMI (continuous)					1.04 (0.99–1.09)	0.11
Liver fat (every 10 HU)					1.07 (0.93–1.23)	0.32
Pre-metabolic syndrome-1					2.39 (1.23–4.62)	0.010
Pre-metabolic syndrome-2					3.88 (2.00–7.52)	< 0.001
Current smoker					1.43 (1.05–1.94)	0.022
Ethanol intake ≥ 20 g/day					0.80 (0.57–1.13)	0.21
Physical activity					0.64 (0.40–1.03)	0.068

Poisson regression models with robust variance were used to estimate the RR, 95% CIs, and P-values.

HU, Hounsfield units; P-S, difference between pancreatic and splenic attenuations in unenhanced computed tomography.

Table 3. Risk ratios (RRs) and 95% CIs for the association between baseline pancreatic fat amounts [–(P-S) tertiles] and incidence of meeting each criterion of metabolic syndrome during the follow-up period

	Central obesity 24.2% (55 / 227)	Elevated BP 39.3% (84 / 214)	Elevated FPG 30.6% (81 / 265)	Elevated TG 36.5% (101 / 277)	Reduced HDL-C 19.2% (59 / 308)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Low pancreatic fat	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate pancreatic fat	0.70 (0.35–1.38) P = 0.30	1.12 (0.74–1.69) P = 0.59	1.50 (0.91–2.47) P = 0.11	1.13 (0.72–1.77) P = 0.59	2.39 (1.05–5.44) P = 0.038
High pancreatic fat	1.14 (0.62–2.10) P = 0.68	0.91 (0.58–1.43) P = 0.69	1.23 (0.71–2.13) P = 0.45	1.44 (0.95–2.20) P = 0.089	3.68 (1.61–8.40) P = 0.002

The incidence of meeting each criterion during follow-up is shown below each criterion. Poisson regression models with robust variance were used to estimate the RR, 95% CIs, and P-values with adjusting for potential confounders: age, sex, BMI, liver fat, current smoking, ethanol intake ≥ 20 g/day, and physical activity.

BP, Blood pressure; FPG, Fasting plasma glucose; TG, Triglycerides; HDL-C, high-density lipoprotein cholesterol; P-S, difference between pancreatic and splenic attenuations in unenhanced computed tomography.

Figure legends

Figure 1

Study flow diagram. Participants with missing data for the factors used in the multivariate analyses were excluded. “Any follow-up” participants (n = 664) received varying numbers of subsequent health checks for the following <6-year period. Annual follow-up participants (n = 320) received annual health checks each year for 4–5 years (eligible for inclusion in the primary analysis).

Figure 1

