Lack of Independent Association Between Fatty Pancreas and Incidence of Type 2 Diabetes: 5-Year Japanese Cohort Study

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OBJECTIVE

Previous cross-sectional studies have shown that attenuation in the pancreas seen on unenhanced computed tomography (CT) scans was inversely correlated with histologic pancreatic fat, and that fatty pancreas was associated with type 2 diabetes mellitus (T2DM). However, no longitudinal study has evaluated whether fatty pancreas increases the incidence of T2DM. We conducted a cohort study to investigate the association between fatty pancreas and the incidence of T2DM.

RESEARCH DESIGN AND METHODS

A total of 813 participants without diabetes underwent health checks by unenhanced CT scanning in 2008 and 2009, and were observed for a median follow-up period of 5.06 (interquartile range 3.01–5.92) years. Attenuation in three regions of the pancreas seen on an unenhanced CT scan was measured, and the mean pancreatic attenuation was calculated to evaluate fatty pancreas at baseline; the more severe the fatty pancreas, the lower the mean pancreatic attenuation. The incident T2DM hazard ratios (HRs) for the association between fatty pancreas and T2DM incidence were estimated by Cox proportional hazards models adjusted for age, sex, BMI, liver attenuation seen on unenhanced CT scan, and alcohol intake of ≥20 g/day.

RESULTS

T2DM occurred in 62 participants (7.6%) during the follow-up period. The higher pancreas attenuation (i.e., less pancreatic fat) at baseline was associated with decreased T2DM incidence in a univariate analysis (crude HR 0.97 [95% CI 0.96–0.99]); and fatty pancreas (lower pancreas attenuation) was positively associated with increased T2DM incidence. However, the association was substantially explained by the confounders (multivariate HR 1.00 [95% CI 0.98–1.02]).

CONCLUSIONS

Fatty pancreas was not independently associated with future T2DM.

Obesity has increased dramatically in recent decades and has become a major public health problem worldwide because it is associated with various diseases such as metabolic syndrome, type 2 diabetes (T2DM), cardiovascular disease, and some types of cancers (1–3). Obesity leads to ectopic fat accumulation in several organs

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such as the liver and pancreas (3,4). Nonalcoholic fatty liver disease (NAFLD) has been vigorously researched, and NAFLD has been shown to be a risk factor for hepatic complications, such as liver cirrhosis and hepatocellular carcinoma, as well as for extrahepatic complications, namely, metabolic syndrome, T2DM, and cardiovascular disease (5–8). Fatty pancreas, or pancreatic fat accumulation, has also been noted recently in relation to T2DM. It is speculated that fatty pancreas induces β-cell dysfunction, leading to T2DM (3). The possible mechanisms of fatty pancreas–induced β-cell dysfunction are lipotoxicity and paracrine effect; an excess amount of triglycerides in pancreatic β-cells causes lipotoxicity and lipoapoptosis in β-cells; and intrapancreatic adipocytes have a negative paracrine effect on β-cells, leading to β-cell dysfunction (3,9).

Previous cross-sectional studies (10,11) have revealed the independent association between ultrasonography (US)-detected fatty pancreas and T2DM after adjusting for confounding factors such as cardiometabolic risk factors. A population-based study (4) using fat-water MRI showed that fatty pancreas was independently associated with increased insulin resistance (IR). In addition, other studies using MRI (12,13) have shown that fatty pancreas was independently associated with β-cell dysfunction. The independent association between fatty pancreas and β-cell dysfunction has also been shown in an unenhanced computed tomography (CT)–based study (14). On the other hand, a recent study using MRI (15) has shown that fatty pancreas was not related to prediabetes or T2DM. However, all of the previous studies mentioned above were cross-sectional studies (4,10–15), and it remains unknown whether fatty pancreas increases T2DM incidence. Therefore, a longitudinal study is warranted to clarify the association between fatty pancreas and T2DM incidence.

Several modalities such as US, endoscopic US, MRI, and unenhanced CT scanning have been used to evaluate pancreatic fat accumulation (4,10–16); however, there is neither a widely accepted modality nor a cutoff point to diagnose fatty pancreas (3). Recently, Kim et al. (17) have reported that pancreatic attenuation on unenhanced CT scans inversely correlated well with histological pancreatic fat accumulation in surgical specimens. CT scanning is considered to be a reliable modality for the quantification of pancreatic fat (17,18).

In this 5-year retrospective cohort study, we investigated whether fatty pancreas is an independent risk factor for incident T2DM on the basis of CT scan evaluation.

RESEARCH DESIGN AND METHODS

Subjects

A retrospective cohort study was conducted to investigate whether fatty pancreas increases T2DM incidence at Keijinkai Maruyama Clinic (Sapporo, Japan). Voluntary health checks are common in Japan, and a total of 1,055 participants underwent a health check by unenhanced CT scanning between 2008 and 2009 (i.e., baseline health check) upon their request. Among the 1,055 participants, 946 participants were included in the current study after exclusion by fasting plasma glucose level ≥126 mg/dL (n = 62), hemoglobin A_{1c} (HbA_{1c}) level ≥6.5% (48 mmol/mol) (n = 65), self-reported physician-diagnosed diabetes (n = 72), having any medication for diabetes (n = 51), pancreatic atrophy (n = 4), space-occupying lesions in the pancreas (n = 1), status postpancreatic resection (n = 1), status postsplenic resection (n = 1), and ambiguous pancreatic margin (n = 1). The participants with an ambiguous pancreatic margin and pancreatic atrophy were excluded as it was not possible to measure the pancreatic attenuation. Some participants met more than one exclusion criterion. An experienced radiologist who had no knowledge of the participants' information reviewed the unenhanced CT images and decided on the participants who should be excluded on the basis of the unenhanced CT images. Among the 946 participants, 813 participants voluntarily underwent repeat health checks after the baseline health check. The follow-up rate was 85.9% (813 of 946 participants). The median follow-up period was 5.06 years (interquartile range 3.01–5.92 years). The study flow diagram is shown in Fig. 1.

Fatty Pancreas and Fatty Liver

Fatty pancreas and fatty liver were assessed by attenuation (in Hounsfield units [HU]) in the pancreas and liver as seen on unenhanced CT scans at baseline; the more severe the fatty pancreas and fatty liver, the lower the attenuation in the pancreas and liver (17,19). The attenuation in the spleen was also evaluated as a previous study (17) used both the difference between the pancreas and spleen attenuation (P − S) and the ratio of the pancreas to spleen attenuation (P/S) for the evaluation of fatty pancreas. Unenhanced CT scanning was performed using a single helical scanner (Asteion KG [TSX-021B]; Toshiba, Otawara, Japan). All measurements using this scanner were performed at comparable scanner settings of 120 kVp, fixed 170 mAs, 10 mm collimation, a pitch of 1.0, and a 10-mm reconstruction interval. Pancreatic, hepatic, and splenic attenuations were measured by seven experienced technicians who had no knowledge of detailed information about the participants and were under the supervision of an experienced radiologist on a workstation (TWS-5000; Toshiba). The three round regions of interest (ROIs) with areas of 1.0 cm^2 were placed on the pancreatic head, body, and tail for the measurement of pancreatic attenuation using unenhanced CT scans; and the mean pancreatic attenuation of the three ROIs was calculated. ROIs were set on the thick part of the pancreatic head, body, and tail as much as possible to minimize the partial volume effect. Similarly, the mean hepatic attenuation was calculated by the placement of three ROIs with areas of 1.0 cm^2 on the hepatic left lobe, anterior segment, and posterior segment using unenhanced CT scans. In addition, the mean splenic attenuation was calculated by the placement of three ROIs with an area of 1.0 cm^2 on the largest slices of the spleen.

T2DM Incidence

The participants who met any of the following four factors were considered to have T2DM: fasting plasma glucose level ≥126 mg/dL, HbA_{1c} level ≥6.5% (48 mmol/mol), self-reported physician-diagnosed diabetes, or receiving any medication for diabetes. HbA_{1c} level was measured using the scale of the Japan Diabetic Society (JDS) in 2008–2012, and using the scale of the National Glycohemoglobin Standardization Program (NGSP) in 2012–2015. We have converted HbA_{1c} (JDS) measured in 2008–2012 to HbA_{1c} (NGSP) using the following

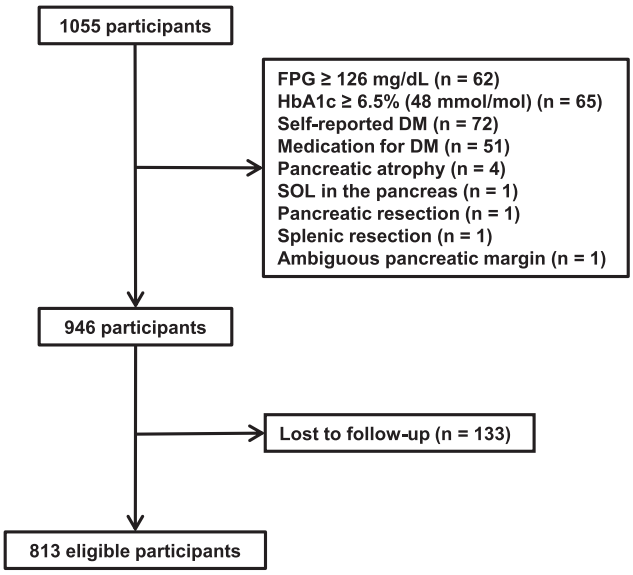

Figure 1—Study flow diagram. Some participants met more than 1 exclusion criterion. DM, diabetes mellitus; FPG, fasting plasma glucose; SOL, space-occupying lesion.

formula: HbA_{1c} (NGSP) (%) = HbA_{1c} (JDS) (%) + 0.4% (20). HbA_{1c} level is shown using the NGSP scale in the current study.

Medical Evaluation

The participants filled out questionnaires about their medical history, medication, family history of diabetes, alcohol drinking habits, smoking cigarettes, and physical exercise. BMI was estimated as the weight (in kilograms) divided by the square of the height (in meters). Dyslipidemia was confirmed when any of the following four factors were met: high triglyceride level (≥150 mg/dL), decreased HDL cholesterol level (<40 mg/dL), elevated LDL cholesterol level (≥140 mg/dL), or self-reported physician-diagnosed dyslipidemia. Hypertension was diagnosed when the participants met any of the following two factors: elevated systolic or diastolic blood pressure (≥140/90 mmHg) or self-reported physician-diagnosed hypertension. Both the amount and frequency of alcohol consumption were questioned in terms of drinking habits. Participants who had continued physical exercise more than twice a week for more than a year were categorized as "physically active."

Statistical Analysis

Data for the baseline characteristics were expressed as the mean ± SD. The association between fatty pancreas and T2DM incidence was evaluated to assess whether fatty pancreas was a significant risk factor for T2DM; specifically, it was investigated whether pancreas attenuation seen on an unenhanced CT scan was independently associated with T2DM incidence. Cox proportional hazards models were used to estimate the crude hazard ratios (HRs), multivariate adjusted HRs, and 95% CIs for the association between pancreas attenuation (an indicator of fatty pancreas) at baseline and T2DM incidence. In the multivariate analysis, age, sex, BMI, liver attenuation (an indicator of fatty liver), and alcohol intake ≥20 g/day were adjusted.

Sensitivity analysis was conducted using the following three other indicators for fatty pancreas: *1*) P − S; *2*) P/S ratio; and *3*) quartile pancreatic attenuation. Both P − S and P/S ratio were used because these parameters were significantly correlated with the histologic pancreatic fat fraction in a previous study (17). Moreover, the 813 eligible participants were divided into a reference group (n = 202), a mild group (n = 202), an intermediate group (n = 205), and a severe group (n = 204) based on quartile pancreas attenuation seen on unenhanced CT scans in descending order. Participants in the severe group, who had the lowest pancreas attenuation seen on unenhanced CT scans, were considered to have the largest amount of fat in their pancreas, whereas participants in the reference group, who had the highest pancreas attenuation seen on unenhanced CT scans, were considered to have the least pancreatic fat (17). As there is no defined cutoff for fatty pancreas (3), the participants with the highest pancreas attenuation were regarded as the reference group.

Further analyses were conducted to clarify which factor confounded the association between fatty pancreas and T2DM incidence the most. Moreover, considering the difference in fat accumulation among the pancreatic head, body, and tail, the association between fatty pancreas in each segment and T2DM incidence was also evaluated on the basis of attenuation in the pancreatic head, body, and tail, separately.

To assess interobserver variability, 50 participants were randomly selected, and an independent radiologist assessed attenuation in the pancreas, liver, and spleen on an unenhanced CT scan for confirmation in the same manner. Pearson correlation coefficients between the data from technicians with an experienced radiologist and the other data for confirmation from the independent radiologist were calculated.

For the purpose of evaluating selection bias, baseline characteristics were compared between participants with and without follow-up. The Student t test and χ^2 test were used to analyze continuous and categorical variables, respectively.

A P value of <0.05 was considered to indicate a statistically significant difference. A categorical indicator for missing responses (missing category) was created, and dummy variables were used for missing data. For statistical analyses, SAS version 9.3 (SAS Institute, Cary, NC) was used.

Ethical Considerations

The current study was approved by the ethics committee of Teine Keijinkai Hospital. Informed consent was not required because this research used a retrospective study design.

RESULTS

Baseline Characteristics

Table 1 shows the baseline data of the study participants. Their mean age was 51.8 ± 9.8, and 627 (77.1%) were men. The mean BMI was 24.0 ± 3.3 kg/m^2. The attenuations of the pancreatic head, body, and tail were 46.9 ± 11.5, 46.4 ± 9.8, and 44.7 ± 10.4 HU, respectively. The mean pancreas attenuation

Table 1—Baseline characteristics

	All participants (n = 813)
Age (years)	51.8 ± 9.8
Sex, men/women (n)	627/186
BMI (kg/m^2)	24.0 ± 3.3
Waist circumference (cm)	85.9 ± 8.5
Amylase (IU/L)	72.1 ± 27.7
Creatinine (mg/dL)	0.74 ± 0.16
AST (units/L)	24.6 ± 14.3
ALT (units/L)	27.4 ± 18.4
GGT (units/L)	55.1 ± 59.0
Albumin (g/dL)	4.3 ± 0.23
FPG (mg/dL)	91.9 ± 9.7
HbA_{1c} (%)	5.2 ± 0.32
HbA_{1c} (mmol/mol)	33 ± 3.5
IFG, n (%)	159 (19.6)
Pancreas attenuation (HU)	46.0 ± 9.5
Liver attenuation (HU)	62.9 ± 9.3
Family history of DM, n (%)	144 (17.7)
Dyslipidemia, n (%)	397 (48.8)
Hypertension, n (%)	193 (23.7)
Alcohol intake ≥20 g/day	241 (29.6)
Current smoker, n (%)	268 (33.3)
Physical exercise, n (%)	163 (20.0)

Continuous data are expressed as mean ± SD, unless otherwise indicated. Pancreas attenuation indicates the mean attenuation of the pancreatic head, body, and tail on an unenhanced CT scan. Liver attenuation indicates the mean attenuation of the hepatic left lobe, anterior segment, and posterior segment. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; FPG, fasting plasma glucose; GGT, γ-glutamyltransferase; IFG, impaired fasting glucose.

was 46.0 ± 9.5 HU. Supplementary Fig. 1 shows the distribution of the mean pancreas attenuation. Most of the participants have a pancreas attenuation of >40 HU.

Association Between Fatty Pancreas and T2DM Incidence

T2DM occurred in 62 participants (7.6%) during the median follow-up period of 5.06 years (interquartile range 3.01–5.92 years). Table 2 shows the HRs and 95% CIs for the association between fatty pancreas and T2DM incidence based on pancreas attenuation. Higher pancreas attenuation (less pancreatic fat) at baseline was associated with decreased T2DM incidence in univariate analysis (crude HR 0.97 [95% CI 0.96–0.99]); fatty pancreas (lower pancreas attenuation) was associated with increased T2DM incidence. However, the association was not evident after adjusting for age, sex, BMI, liver attenuation, and alcohol intake of ≥20 g/day (multivariate adjusted HR 1.00 [95% CI 0.98–1.02]). The association between fatty pancreas and T2DM incidence was explained by the confounders.

Sensitivity Analysis

P − S, P/S ratio, and quartile pancreas attenuation (categorical data) were used as indicators of fatty pancreas instead of pancreas attenuation (continuous data). The results are shown in Table 3. The multivariate adjusted HRs for the association between fatty pancreas and T2DM incidence were 1.00 (95% CI 0.98–1.02) and 1.07 (95% CI 0.29–3.92) in P − S and P/S, respectively. There was no independent association between fatty pancreas and T2DM incidence. Based on quartile pancreatic attenuation, the incidence of T2DM increased with the severity of fatty pancreas at baseline, as follows: 5.0% (10 of 202 participants), 5.9% (12 of 202 participants), 8.3% (17 of 205 participants), and 11.3% (23 of 204 participants) of participants, respectively, in the reference, mild, intermediate, and severe groups. Compared with the reference group, the crude HRs were 1.21 (95% CI 0.51–2.87), 1.74 (95% CI 0.78–3.89), and 2.44 (95% CI 1.13–5.27), respectively, in the mild, intermediate, and severe groups. However, the association was not found in the multivariate analysis. The multivariate adjusted HRs between fatty pancreas and T2DM incidence were 0.92 (95% CI 0.39–2.18), 1.18 (95% CI 0.54–2.60), and 1.03 (95% CI 0.47–2.23), respectively, in the mild, intermediate, and severe groups. These sensitivity analysis results confirmed that there was no independent association between fatty pancreas and T2DM incidence.

Confounding Factors

To clarify which factor explains the association between fatty pancreas and T2DM incidence the most, further analyses were conducted in an age- and sex-adjusted model (Supplementary Table 1). Each covariate was added to the age- and sex-adjusted model, and the results showed that both BMI and fatty liver explained the association the most. The multivariate adjusted HR was 0.99 (95% CI 0.97–1.02) after adjusting for age, sex, and BMI. After adjusting for age, sex, and liver attenuation, the multivariate adjusted HR was 0.99 (95% CI 0.97–1.02). The positive association between fatty pancreas and T2DM incidence was substantially explained by BMI and liver attenuation.

Association Between Fatty Pancreas in Each Segment and T2DM Incidence

Attenuation in the pancreatic head, body, and tail was assessed on an unenhanced CT scan, and the association between fatty pancreas in each segment and T2DM incidence was separately evaluated. The results are shown in Supplementary Table 2. The multivariate adjusted HRs for the association between fatty pancreas in each segment and T2DM incidence were 1.01 (95% CI 0.99–1.03), 1.00 (95% CI 0.98–1.02), and 0.99 (95% CI 0.97–1.01), respectively, in the pancreatic head, body, and tail. There was no independent association between fatty pancreas and T2DM incidence in any segment of the pancreas.

Interobserver Variability

Pearson correlation coefficients between the data from technicians with an experienced radiologist and the other data for confirmation from the other radiologist were as follows: pancreatic head 0.81; pancreatic body 0.90; pancreatic tail 0.88; hepatic left lobe 0.94; hepatic anterior segment 0.97; hepatic posterior segment 0.97; and spleen 0.81. The results showed a significantly high correlation (all P values were <0.001).

Baseline Characteristics of Participants With and Without Follow-up

To evaluate selection bias, the baseline characteristics of the participants without follow-up were compared with those of the participants with follow-up. The results are shown in Supplementary Table 3. There were more women among the participants without follow-up than with follow-up (31.6% vs. 22.9%, P = 0.030). Moreover, the participants without follow-up had a lower γ-glutamyltransferase level (46.4 ± 43.1 vs. 55.1 ± 59.0, P = 0.044) and less impaired fasting glucose (11.3% vs. 19.6%, P = 0.022) at baseline than the participants with follow-up, but the other factors were not significantly different between them.

Table 2—HRs and 95% CIs for the association between fatty pancreas and T2DM incidence, based on pancreas attenuation

	All of the participants (n = 813)					
	Crude		Age and sex adjusted		Multivariate adjusted	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Pancreas attenuation (continuous)	0.97 (0.96–0.99)	0.0046	0.98 (0.96–1.00)	0.047	1.00 (0.98–1.02)	0.95
Age (continuous)			1.02 (0.99–1.04)	0.29	1.04 (1.01–1.07)	0.021
Men			2.84 (1.13–7.13)	0.027	1.76 (0.69–4.50)	0.24
BMI (continuous)					1.18 (1.08–1.29)	<0.001
Liver attenuation (continuous)					0.95 (0.93–0.97)	<0.001
Alcohol intake ≥20 g/day					1.43 (0.82–2.49)	0.20

Cox proportional hazards models were used to estimate the HRs, 95% CIs, and *P* values. Fatty pancreas was assessed by attenuation in the pancreas on unenhanced CT at baseline; the more severe the fatty pancreas, the lower the attenuation in the pancreas.

CONCLUSIONS

This 5-year retrospective cohort study of 813 participants showed that fatty pancreas at baseline was associated with an increased incidence of T2DM. However, the association was not evident after adjusting for potential confounders (i.e., age, sex, BMI, and liver attenuation seen on unenhanced CT scan, and alcohol intake of ≥20 g/day). Both obesity and fatty liver are well-established risk factors for T2DM (7,21,22). In the context of these results, fatty pancreas was not independently associated with future T2DM.

Our results were consistent with the results of a recent cross-sectional study using MRI (15) but not with previous studies based on US (10,11), which showed an independent association between fatty pancreas and T2DM after adjusting for cardiometabolic factors. Wang et al. (11) showed that fatty pancreas was independently associated with T2DM in 8,097 participants (odds ratio 1.59 [95% CI 1.30–1.95]). Ou et al. (10) also reported a significant association between fatty pancreas and T2DM in 7,464 participants (odds ratio 1.34 [95% CI 1.07–1.68]). The discrepancy between the previous studies and the current study can be explained by the difference in the imaging modality (i.e., US vs. CT scan) and study design (i.e., cross-sectional vs. longitudinal study). US provides qualitative rather than quantitative assessment of fat infiltration (23), and it is not always possible to evaluate the entire pancreas on US, owing to bowel gas or obesity (3,4,17). On the other hand, CT scanning easily provides the entire image of the pancreas, and it has been shown as a histologically proven modality that enables the quantitative assessment of pancreatic fat (17,18). The current study used a longitudinal cohort study, whereas all of the previous studies on this topic were limited to cross-sectional studies. When discussing causal relationships, a longitudinal study design is preferred over a cross-sectional study design because longitudinal research can help to establish lines of evidence for both covariations between variables and the temporal order of variables; it can enhance causal inference. To our knowledge, the current

Table 3—Multivariate-adjusted HRs and 95% CIs for the association between fatty pancreas and T2DM incidence, evaluated by P − S, P/S ratio, and quartile of pancreatic attenuation

	All of the participants (n = 813)					
	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
P − S (continuous)	1.00 (0.98–1.02)	0.93				
P/S (continuous)			1.07 (0.29–3.92)	0.92		
Reference group					1.00 (reference)	
Mild group					0.92 (0.39–2.18)	0.85
Intermediate group					1.18 (0.54–2.60)	0.68
Severe group					1.03 (0.47–2.23)	0.95
Age (continuous)	1.04 (1.01–1.07)	0.018	1.04 (1.01–1.07)	0.018	1.04 (1.01–1.07)	0.022
Men	1.77 (0.69–4.52)	0.23	1.77 (0.69–4.52)	0.23	1.75 (0.69–4.49)	0.24
BMI (continuous)	1.18 (1.09–1.29)	<0.001	1.18 (1.09–1.29)	<0.001	1.18 (1.08–1.28)	<0.001
Liver attenuation (continuous)	0.95 (0.93–0.97)	<0.001	0.95 (0.93–0.97)	<0.001	0.95 (0.93–0.97)	<0.001
Alcohol intake ≥20 g/day	1.43 (0.82–2.48)	0.20	1.43 (0.82–2.48)	0.21	1.42 (0.82–2.47)	0.21

Model 1, model 2, and model 3 were based on the P − S, P/S ratio, and quartile pancreatic attenuation, respectively. Cox proportional hazards models were used to estimate the HRs, 95% CIs, and *P* values. Spleen attenuation was used as a control in model 1 and model 2. In model 3, all of the participants were divided into the reference group, mild group, intermediate group, and severe group on the basis of quartile pancreas attenuation on unenhanced CT scanning in descending order. The participants in the severe group, who had the lowest pancreas attenuation seen on CT scanning, were considered to have the largest amount of fat in the pancreas, whereas the participants in the reference group, who had the highest pancreas attenuation seen on CT scanning, were considered to have the lowest amount of fat in the pancreas.

study is the first longitudinal study to examine the association between fatty pancreas and T2DM. The study showed the absence of an independent association between fatty pancreas and T2DM incidence.

Previous studies (4,12–14) have reported an increased IR and β-cell dysfunction in fatty pancreas. Wong et al. (4) conducted an MRI-based cross-sectional study, which included 685 participants, to evaluate IR and β-cell function on fatty pancreas using the HOMA-IR and HOMA-β, respectively. They concluded that pancreatic fat was independently associated with only HOMA-IR after adjusting for hepatic fat and BMI (4). Tushuizen et al. (12) reported that β-cell glucose sensitivity was independently associated with MRI-assessed pancreatic fat in 24 participants without diabetes after adjusting for age, BMI, fasting plasma glucose level, and triglyceride level. Heni et al. (13) showed that pancreatic fat assessed on MRI was inversely associated with oral glucose tolerance test–based measures of insulin secretion in 23 participants with impaired fasting glucose and/or impaired glucose tolerance after adjustment for visceral adipose tissue. Yokota et al. (14) conducted an unenhanced CT-based study, which included 167 participants and showed that pancreatic fat was significantly associated with insulinogenic index (i.e., an indicator of insulin secretion) after adjusting for age, sex, BMI, waist circumference, and lipid profile. These studies (4,12–14) indicate that fatty pancreas might cause an increased IR and β-cell dysfunction, leading to T2DM. However, all of these reports (4,12–14) were cross-sectional studies, and proper confounders such as fatty liver were not always adjusted. Our longitudinal study examined the association between fatty pancreas and T2DM incidence after adjusting for the proper confounders, although it lacked information on IR or β-cell dysfunction. Further research is warranted to clarify the effects of fatty pancreas on IR and β-cell dysfunction.

At present, it remains unknown whether fatty pancreas is a pathologic condition that causes metabolic syndrome (3). Lee et al. (24) showed that 76.9% of participants (80 of 104 participants) with metabolic syndrome had US-detected fatty pancreas. Wu and Wang (25) conducted a US-based cross-sectional study showing that 34.7% of participants (25 of 72 participants) with fatty pancreas and 17.5% of participants (85 of 485 participants) with nonfatty pancreas had metabolic syndrome. Although a close association between fatty pancreas and metabolic syndrome has been shown, the causal relationship remains unproven; fatty pancreas might not be independently associated with an incidence of metabolic syndrome that was similar to that for T2DM. Further research is necessary to clarify the effects of fatty pancreas on future metabolic syndrome.

The current study has several limitations. First, this was a 5-year retrospective cohort study conducted in a single center involving an Asian population. The follow-up period of 5 years might not be sufficient to evaluate the association between fatty pancreas and T2DM incidence, and the pathophysiology of T2DM may vary in different ethnicities (26). Therefore, similar studies with a longer follow-up period in other populations are needed to verify our results. Second, there were no data about HOMA-IR, HOMA-β, oral glucose tolerance test, and glucose clamp technique, which evaluate IR and β-cell dysfunction. Further research is warranted to clarify the effects of fatty pancreas on IR and β-cell dysfunction. Third, the study participants voluntarily underwent a health check, including an unenhanced CT scan. Thus, they might be more health conscious and healthier than the general population. A previous Japanese population–based cohort study (27) showed a 5-year T2DM incidence rate of 5.7% (125 of 2,207 participants), which was not substantially different from the T2DM incidence rate for the current study of 7.6% (62 of 813 participants). The participants in the current study are considered to be representative in terms of T2DM. Unfortunately, there are no data on fatty pancreas incidence in the general Japanese population, and it is difficult to compare the difference between our participants and the general Japanese population with regard to fatty pancreas. Fourth, attenuation in the pancreas and liver seen on CT scan is affected not only by fat infiltration, but by also other components, such as manganese and iron (17,28). Recent MRI-based techniques are considered to be superior to CT scanning in detecting fat accumulation in the pancreas and liver (3,29); however, the use of MRI for a large number of participants is hampered by the long acquisition time (17). CT scanning is a more practical modality, and the correlation between CT scan–evaluated fat and histologic fat in the pancreas and liver has been established (17–19). Therefore, CT scanning was selected as a modality for evaluating fatty pancreas and fatty liver. Fifth, there were some participants in this study who could not be followed up, although the follow-up rate was relatively high (85.9%). This might have affected our results.

In conclusion, this is apparently the first longitudinal study evaluating the effects of fatty pancreas on T2DM incidence. The study showed that fatty pancreas was associated with T2DM incidence in a crude model, but the association was substantially explained by confounders such as fatty liver and obesity. In the context of the present results, fatty pancreas was not independently associated with future T2DM. Further research is also warranted to evaluate the effect of fatty pancreas on the development of metabolic syndrome.

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approved the manuscript before submission. H.M. 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.

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