The association of liver and pancreatic fat accumulation patterns with diabetes and prediabetes in young and middle-aged Chinese adults

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Abstract

Introduction: The combined role of fatty liver disease (FLD) and pancreatic fat accumulation (PFA) in diabetes is unknown. In the present study, we aimed to evaluate the relationship between the phenotype of FLD and PFA and type 2 diabetes mellitus (T2DM) or prediabetes in young and middle-aged adults.
Material and methods: 6205 adults aged 25–60 years who underwent computed tomography (CT) chest examinations were included in this study. Fatty liver disease was defined based on the ratio of liver CT attenuation and spleen CT attenuation (ratio < 0.8). PFA was defined based on the ratio of pancreatic CT attenuation and spleen CT attenuation (ratio < 0.9). The phenotype of FLD and PFA was divided into three groups: neither FLD nor PFA; either FLD or PFA; both FLD and PFA.
Results: There were 236 patients with T2DM and 242 subjects with prediabetes. 1861 subjects had FLD or PFA, and 190 subjects had both FLD and PFA. Subjects with both FLD and PFA or subjects with either FLD or PFA had higher risk of T2DM or prediabetes than those with neither FLD nor PFA (odds ratio (OR) = 2.61, 95% CI:1.35–5.02; OR = 1.37, 95% CI: 1.00–1.93; OR = 2.76, 95% CI: 1.60–4.790; OR = 1.43, 95% CI: 1.07–1.91). Subjects with both FLD and PFA also had a higher risk of prediabetes and prediabetes + diabetes than those with FLD or PFA alone (OR = 1.66, 95% CI: 1.00–2.88; OR = 1.64, 95% CI: 1.02–2.63).
Conclusions: Subjects with both FLD and PFA had higher risk of T2DM than those with neither condition or either FLD or PFA.

Key words: type 2 diabetes, fatty liver disease, pancreatic fat accumulation, young population, middle-aged population.

Introduction

The association between hepatic fat content and diabetes has been well studied. Hepatic steatosis is characterized by the abnormal and excessive deposition of fat, predominantly triglycerides, in liver tissue [1–3], is strongly linked to insulin resistance and dysregulated glucose metabolism, serving as a key predictor for the development of type 2 diabetes and prediabetes [4, 5]. Studies indicate that individuals with non-alcoholic fatty liver disease exhibit a 2- to 5-fold increased risk of

progressing to type 2 diabetes mellitus (T2DM) compared to those without hepatic steatosis [6]. This relationship arises because ectopic hepatic fat disrupts insulin signaling pathways, impairing the suppression of hepatic glucose production and exacerbating hyperglycemia [7]. Even in prediabetic stages, elevated hepatic fat correlates with early metabolic dysfunction, including reduced insulin sensitivity and abnormal postprandial glycemic responses [8]. Interventions targeting hepatic fat reduction, such as weight loss or pharmacological agents, have demonstrated efficacy in improving glycemic control [9], underscoring hepatic steatosis as both a biomarker and a modifiable driver of diabetes risk.

Recently, pancreatic fat content has garnered significant attention in the context of diabetes and prediabetes due to its potential impact on pancreatic function and glucose metabolism [10]. Increased pancreatic fat deposition has been associated with impaired pancreatic β-cell function [11, 12], which is crucial for insulin secretion and glucose regulation. This fat accumulation may contribute to insulin resistance and reduced insulin sensitivity, both of which are key factors in the progression from prediabetes to type 2 diabetes. Studies have shown a positive correlation between pancreatic fat content, measured by techniques such as magnetic resonance imaging (MRI) or computed tomography (CT), and the risk of developing diabetes and prediabetes [13, 14].

Recent research has separately explored the relationship between diabetes and pancreatic fat, as well as that between diabetes and hepatic fat [4]. However, subjects may have high levels of both pancreatic fat and hepatic fat. The mixed effects of pancreatic fat and hepatic fat on glucose metabolism and diabetes have not been well investigated. We hypothesized that this condition may be associated with a higher risk of diabetes or prediabetes. In the present study we aimed to test this hypothesis in a Chinese population.

Material and methods

Study population

This retrospective cohort study used data from participants aged 25–60 years who underwent annual CT lung cancer screening between 2018 and 2020. Participants had undergone baseline low-dose chest CT scans and had available blood biochemical data. Inclusion criteria: age 25–60 years at baseline; completion of at least one annual lung cancer screening CT scan; availability of fasting blood glucose, lipid profile data and demographic information. Exclusion criteria: history of pancreatic/hepatic lesions, cancer, or metabolic disorders (e.g., chronic pancreatitis, cirrhosis); incomplete CT or biochemical data; poor-quality CT images (e.g., motion artifacts). The flowchart of the study population is shown in Figure 1. Ethics approval was obtained from the Gongli Hospital of Shanghai Pudong New Area (GLYYls2021-008). The study was conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived by the Ethics Committee of Gongli Hospital of Shanghai Pudong New Area because of the retrospective nature of the study.

Blood biochemical data collection

Blood test data were collected from the electronic medical systems. The following data were obtained: fasting plasma glucose (FPG), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albumin, uric acid, creatinine, and aspartate aminotransferase (AST). Diabetes and prediabetes were evaluated according to the following criteria: diabetes – FPG ≥ 126 mg/dl (7.0 mmol/l) or self-reported antidiabetic medi-

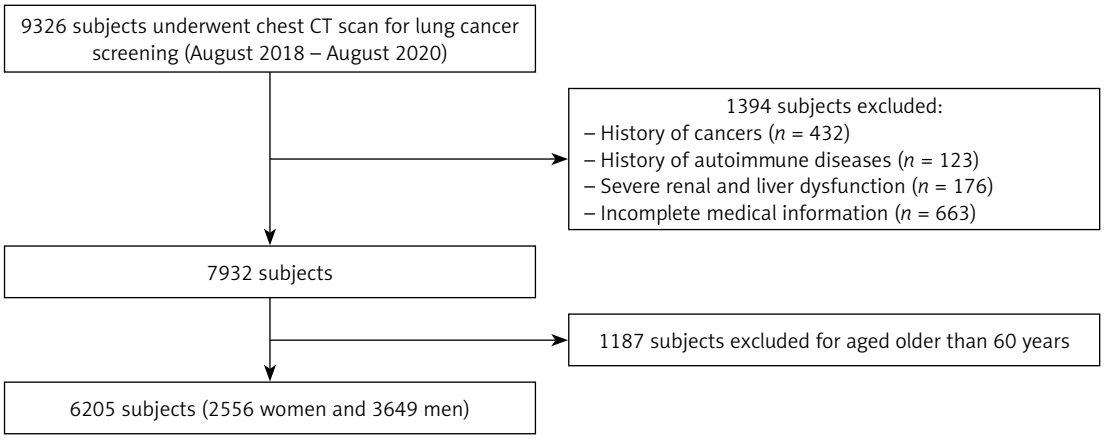

Figure 1. Flowchart of study population

cation use; prediabetes – FPG in the range 110–125 mg/dl (6.1–6.9 mmol/l).

CT-based fat quantification

Pancreatic and hepatic fat content were measured on non-contrast CT scans using Hounsfield Unit (HU)-based thresholds. Liver fat: Regions of interest (ROIs) were placed in three hepatic segments (avoiding vessels/lesions). Mean liver attenuation/spleen attenuation < 0.8 indicates fatty liver disease (FLD). Pancreatic fat accumulation (PFA): ROIs were placed in the pancreatic head, body, and tail. Fat deposition was quantified using validated thresholds, defined as a mean pancreatic attenuation/spleen attenuation ratio < 0.9. All measurements were performed by two blinded radiologists.

Statistical analysis

Data management and statistical analyses were performed using commercial software (SPSS 20.0). Continuous variables (e.g., age, BMI, fat attenuation values) were presented as mean ± standard deviation (if normally distributed) or median (interquartile range) if non-normally distributed. Normality was assessed using the Shapiro-Wilk test. Categorical variables (e.g., sex, diabetes status) were summarized as frequencies and percentages. The independent samples *t*-test was used for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. The χ^2 test or Fisher's exact test was used for categorical data. Multivariable logistic regression was used to assess associations between pancreatic/hepatic fat (independent variables) and diabetes/prediabetes (dependent variables). Model 1 was adjusted for age, sex, and body mass index; Model 2 was further adjusted for liver function, renal function, albumin, uric acid, blood pressure, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Subgroup analyses were performed in men and women, and in subjects with hepatic steatosis or pancreatic steatosis. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

Characteristics of participants

Characteristics of participants are shown in Table I. A total of 6205 subjects – 3649 men and 2556 women – were included in this study. Participants with neither FLD nor PFA were younger than those with either FLD or PFA ($p < 0.01$). The proportion of male patients was higher in participants with both FLD and PFA than in those with neither FLD nor PFA, or either FLD or PFA ($p < 0.01$).

Table I. Characteristics of the subjects divided by phenotype of fatty liver disease and pancreatic fat accumulation

Parameter	Neither FLD nor PFA (*n* = 4154)	FLD or PFA (*n* = 1861)	FLD and PFA (*n* = 190)	*P*-value
Age [years]	42.97 ±9.52	45.2 ±9.40	43.5 ±9.37	< 0.001
Sex [men]	2238 (53.9%)	1249 (67.1%)	162 (85.3%)	< 0.001
BMI [kg/m^2]	25.22 ±2.98	25.84 ±2.08	26.82 ±3.21	0.04
Waist circumference [cm]*	81.46 ±9.65	86.38 ±10.37	89.65 ±11.46	< 0.001
Pancreatic CT attenuation [HU]	49.33 ±3.68	42.66 ±5.92	41.68±6.11	< 0.001
Liver CT attenuation [HU]	57.24 ±6.04	42.33 ±11.79	32.47 ±8.16	< 0.001
AST [U/l]	23.15 ±31.46	25.10 ±11.09	32.11 ±14.61	<0.001
Albumin [mmol/l]	41.86 ±3.06	42.08 ±3.16	42.22 ±2.85	0.02
Uric acid [µmol/l]	300.7 ±94.6	338.51 ±91.4	386.4 ±93.0	< 0.001
Creatinine [mmol/l]	72.85 ±15.19**	75.91 ±14.16	77.91 ±14.47	< 0.001
Blood glucose [mmol/l]	5.05 ±0.99	5.28 ±1.30	5.73 ±1.49	< 0.001
HDL-c [mmol/l]	1.54 ±0.34	1.41±0.33	1.32 ±0.38	< 0.001
LDL-c [mmol/l]	2.96 ±0.79	3.10 ±0.80	3.16 ±0.87	<0.001
TC [mmol/l]	4.70 ±0.92	4.75 ±0.96	4.85 ±1.00	0.008
TG [mmol/l]	1.45 ±1.22	1.78 ±1.59	2.71 ±2.46	<0.001
SBP [mm Hg]	126.27 ±15.26	128.03 ±15.51	129.78±7.53	0.13
DBP [mm Hg]	75.08 ±7.75	76.12 ±8.01	77.58 ±8.13	0.19
Diabetes	116 (2.8%)	95 (5.1%)	25 (13.2%)	< 0.001
Prediabetes	116 (2.8%)	105 (5.6%)	21 (11.1%)	< 0.001

*AST – aspartate aminotransferase, BMI – body mass index, CT – computed tomography, DBP – diastolic blood pressure, HDL-c – high-density lipoprotein cholesterol, HU – Hounsfield unit, LDL-c – low-density lipoprotein cholesterol, SBP – systolic blood pressure, TC – total cholesterol, TG – triglyceride, TYG – triglyceride-glucose. *n = 2136 for neither FLD nor PFA, n = 893 for FLD or PFA and n = 94 for FLD and PFA.*

Table II. Association between fatty liver disease and pancreatic fat accumulation and the risk of diabetes or prediabetes

Parameter	Model 1	*P*-value	Model 2	*P*-value	Model 3	*P*-value
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Diabetes						
Neither FLD nor PFA	1		1		1	
FLD or PFA	1.43 (1.08–1.90)	0.013	1.58 (1.15–2.17)	0.004	1.37 (1.00–1.93)	0.05
FLD and PFA	3.66 (2.24–5.97)	< 0.001	3.15 (1.73–5.74)	< 0.001	2.61 (1.35–5.02)	0.004
Prediabetes						
Neither FLD nor PFA	1		1		1	
FLD or PFA	1.65 (1.26–2.18)	< 0.001	1.50 (1.12–2.00)	0.006	1.43 (1.07–1.91)	0.02
FLD and PFA	3.74 (2.22–6.28)	< 0.001	3.17 (1.86–5.40	< 0.001	2.76 (1.60–4.79)	< 0.001
Diabetes + prediabetes						
Neither FLD nor PFA	1		1		1	
FLD or PFA	1.57 (1.28–1.93)	< 0.001	1.57(1.26–1.97)	< 0.001	1.44 (1.14–1.82)	0.003
FLD and PFA	4.01 (2.72–5.91)	< 0.001	3.33 (2.14–5.17)	< 0.001	2.83 (1.77–4.51)	< 0.001

Model 1 was adjusted for age, sex, and body mass index; Model 2 was further adjusted for liver function, renal function, albumin, uric acid, and blood pressure. Model 3 was further adjusted for low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. CI – confidence interval, FLD – fatty liver disease, HDL – high-density lipoprotein cholesterol, OR – odds ratio, PFA – pancreatic fat accumulation.

Table III. Association between fatty liver disease and pancreatic fat accumulation and the risk of diabetes or prediabetes in men and women

Gender	Parameter	Model 1	*P*-value	Model 2	*P*-value
		OR (95% CI)		OR (95% CI)	
Men	Diabetes				
	Neither FLD nor PFA	1		1	
	FLD or PFA	1.42 (1.03–1.97)	0.034	1.32 (0.89–1.96)	0.16
	FLD and PFA	3.84 (2.27–6.49)	< 0.001	2.97 (1.51–5.83)	0.002
	Prediabetes				
	Neither FLD nor PFA	1		1	
	FLD or PFA	1.62(1.18–2.21)	0.003	1.39 (1.00–1.94)	0.05
	FLD and PFA	3.82 (2.19–6.67)	< 0.001	2.99 (1.66–5.37)	< 0.001
	Diabetes + prediabetes				
	Neither FLD nor PFA	1		1	
	FLD or PFA	1.56 (1.23–1.98)	< 0.001	1.40 (1.07–1.84)	0.014
	FLD and PFA	4.23(2.77–6.45)	< 0.001	3.05 (1.86–5.03)	< 0.001
Women	Diabetes				
	Neither FLD nor PFA	1		1	
	FLD or PFA	1.49 (0.83–2.66)	0.18	1.56 (0.75–3.27)	0.08
	FLD and PFA	2.66 (0.58–12.19)	0.21	0.17 (0.04–7.00)	0.35
	Prediabetes				
	Neither FLD nor PFA	1		1	
	FLD or PFA	1.93 (1.06–3.53)	0.03	1.61 (0.85–3.05)	0.15
	FLD and PFA	3.69 (0.80–17.12)	0.10	1.25 (0.22–7.02)	0.80
	Diabetes + prediabetes				
	Neither FLD nor PFA	1		1	
	FLD or PFA	1.71 (1.11–2.61)	0.014	1.60 (0.97–2.63)	0.06
	FLD and PFA	3.26 (1.04–10.11)	0.04	0.92 (0.16–5.14)	0.92

Model 1 was adjusted for age, sex and body mass index; Model 2 was further adjusted for liver function, renal function, albumin, uric acid, blood pressure, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. CI – confidence interval, FLD – fatty liver disease, HDL – high-density lipoprotein cholesterol, OR – odds ratio, PFA – pancreatic fat accumulation.

The BMI and waist circumference of participants with both FLD and PFA were greater than those of people with neither FLD nor PFA ($p < 0.05$). The pancreatic and liver CT attenuation were significantly higher in participants with neither FLD nor PFA than in those with both FLD and PFA, or either FLD or PFA ($p < 0.01$). Levels of AST, uric acid, creatinine, blood glucose, LDL-c, TC, and TG were higher in participants with both FLD and PFA than in participants with neither FLD nor PFA, or either FLD or PFA ($p < 0.01$). The level of HDL-c was higher in participants without FLD or PFA than in those with both FLD and PFA, or either FLD or PFA ($p < 0.01$). However, no significant differences were found in systolic blood pressure (SBP) or diastolic blood pressure (DBP) between these groups ($p > 0.05$). The prevalence of diabetes and prediabetes in our population were 3.80% and 3.90%, respectively. The prevalence of T2DM or prediabetes in subjects with both FLD and PFA was significantly higher than those with neither FLD nor PFA, or either FLD or PFA ($p < 0.01$).

Association between FLD/PFA and the risk of diabetes or prediabetes

First, we used multivariate logistic regression analyses to identify the association between FLD/PFA and the risk of T2DM or prediabetes (Table II). Having both FLD and PFA, and FLD or PFA, were associated with a high risk of T2DM in all three models. The odds ratio (OR) was 1.37 (95% confidence interval (CI): 1.00–1.93) for FLD or PFA alone and 2.61 (95% CI: 1.35–5.02) for both FLD and PFA. Similar associations were found for presence of both FLD and PFA, and FLD or PFA alone, and the risk of prediabetes (OR = 2.76, 95% CI: 1.60–4.790; OR = 1.43, 95% CI: 1.07–1.91). In addition, presence of both FLD and PFA, and FLD or PFA alone, were associated with a high risk of diabetes and prediabetes (OR = 2.83, 95% CI: 1.77–4.51; OR = 1.44, 95% CI: 1.14–1.82).

Subgroup analysis

We also performed subgroup analysis in men and women (Table III). The association between both FLD and PFA and the risk of diabetes or prediabetes in men was the same as that in the overall population. A significant association was found between subjects with both FLD and PFA and the risk of diabetes or prediabetes (diabetes, OR = 2.97, 95% CI: 1.51–5.83; prediabetes, OR = 2.99, 95% CI: 1.66–5.37; diabetes + prediabetes, OR = 3.05, 95% CI:1.86–5.03) in men. Male subjects with FLD or PFA had high risk of prediabetes (OR = 1.39, 95% CI: 1.00–1.94) and risk of diabetes and prediabetes (OR = 1.40, 95% CI: 1.07–1.84), but not high risk of diabetes. However, no significant association was observed between FLD/PFA and the risk of diabetes or prediabetes after full adjustment in women.

We subsequently evaluated the association between FLD/PFA and the risk of T2DM or prediabetes in subjects with FLD or PFA (Table IV). Subjects with both FLD and PFA had a higher risk of prediabetes and prediabetes + diabetes than those with FLD or PFA alone (OR = 1.66, 95% CI: 1.00–2.88; OR = 1.64, 1.02–2.63).

Discussion

Studies have shown that fat accumulation in intra-abdominal [15], hepatic [16], pancreatic [14], and skeletal muscle [17] is associated with the risk of developing type 2 diabetes. However, most recent studies have mainly focused on one fat distribution pattern. Distinct body fat distribution patterns may determine the likelihood of developing type 2 diabetes in certain individuals [10, 17]. In

Table IV. Association between fatty liver disease and pancreatic fat accumulation and the risk of diabetes or prediabetes in subjects with FLD or PFA

Parameter	Model 1	*P*-value	Model 2	*P*-value	Model 3	*P*-value
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Diabetes						
FLD or PFA	1		1		1	
FLD and PFA	2.44 (1.49–4.00)	< 0.001	1.89 (1.03–3.46)	0.039	1.73 (0.90–3.32)	0.10
Prediabetes						
FLD or PFA	1		1		1	
FLD and PFA	2.14 (1.27–3.63)	0.004	1.82 (1.05–3.13)	0.032	1.66 (1.00–2.88)	0.05
Diabetes + prediabetes						
FLD or PFA	1		1		1	
FLD and PFA	2.39 (1.61–3.54)	< 0.001	1.82 (1.16–2.86)	0.009	1.64 (1.02–2.63)	0.04

Model 1 was adjusted for age, sex, and body mass index; Model 2 was further adjusted for liver function, renal function, albumin, uric acid, and blood pressure. Model 3 was further adjusted for low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. CI – confidence interval, FLD – fatty liver disease, HDL – high-density lipoprotein cholesterol, OR – odds ratio, PFA – pancreatic fat accumulation.

the present study, we evaluated the risk of diabetes or prediabetes in subjects with different patterns of hepatic and pancreatic fat accumulation. Our data demonstrated that subjects with hepatic or pancreatic fat accumulation had high risk of diabetes or prediabetes. Moreover, our study further reported that individuals with both hepatic and pancreatic fat accumulation had higher probability of prediabetes and prediabetes + diabetes than those with FLD or PFA alone.

A few studies have analyzed the association between multiple fat compartments and risk of diabetes [4, 18, 19]. Yamazaki *et al.* reported the association between four fat distribution clusters and incident diabetes [16]. They found that subjects in hepatic steatosis and pancreatic steatosis clusters had high likelihood of diabetes compared with those with steatopenia after adjusting for age, sex, BMI, smoking and drinking habits, blood pressure, serum lipids, and anti-hypertension/anti-diabetic medicine. Moreover, they observed an interaction between pancreatic fat and hepatic fat, visceral fat, and muscle fat [4]. This study indicated the role of pancreatic fat in diabetes. However, the hepatic steatosis cluster included subjects with high levels of liver fat and visceral fat, and the pancreatic steatosis clusters included subjects with high levels of pancreatic fat, visceral fat, and muscle fat. Yamazaki's study did not include the cluster of high pancreas fat and liver fat. To our knowledge, our study may be first one to show the association of diabetes or prediabetes and the cluster of high pancreatic fat and liver fat.

The core pathophysiology of diabetes and prediabetes is insulin resistance and β-cell dysfunction [20]. Insulin resistance refers to a decreased responsiveness of body cells – especially muscle, fat, and liver cells – to the normal action of insulin. β-cell dysfunction, characterized by relative insulin insufficiency and/or aberrant secretory patterns, causes persistent hyperglycemia. High levels of hepatic fat may lead to diabetes through hepatic and systemic insulin resistance, which may be achieved either through direct effects on hepatocytes or through the effects of liver-derived factors on distal organs [4, 15, 21]. High levels of pancreatic fat may influence insulin secretion [4, 13, 14, 22]. The DAG activated protein kinase C epsilon (PKCε) generated from pancreatic fat breakdown inhibits insulin gene transcription [23]. The elevated RBP4 secreted by pancreatic adipose tissue induces insulin resistance in β-cells via the JNK pathway [24]. In addition, the effects of pancreatic fat on insulin secretion may be modified by genetic factors [22]. Organ-organ communication may also play a role in modulating insulin secretion [4, 25]. Our data showed that the detrimental effects of liver fat do not act alone but in concert with pancreatic fat. Excise, diet, and physical activity are important strategies for reducing excessive liver fat deposition [26–29]. Exercise may affect inflammatory and oxidative markers, as well as lipid levels [30, 31].

Our results showed associations between FLD and/or PFA and diabetes or prediabetes mainly in men. One important reason is the small sample size in female subjects with both FLD and PFA. There were 25 cases of diabetes in subjects with both FLD and PFA. Among female subjects, there were fewer than 10 cases of diabetes. Therefore, further studies are needed to investigate the associations between FLD or/and PFA and diabetes or prediabetes in the female population.

Our study has several advantages. The study enrolled a large sample of 6,326 subjects. Our study may be the first one to identify the association between liver and pancreatic fat content and diabetes or prediabetes in young and middle-aged adults. Our study has several limitations. First, it was a cross-sectional study. It did not reveal a causal relationship between hepatic and/or pancreatic fat accumulation and risk of diabetes. Longitudinal or prospective studies are required to demonstrate the causal relationship. Second, fat accumulation in the liver and pancreas were evaluated by CT. MRI may be more accurate for quantitative determinants of fat content. However, CT-based fat measurements have also been widely used [4, 32]. Third, we did not control for all possible confounders, such as smoking and drinking habits. Finally, this was a single center study with a Chinese population. The generalizability of the findings requires validation in multi-center and multi-ethnic populations.

In conclusion, we found that elevated pancreatic and hepatic fat content were associated with a significantly increased risk of type 2 diabetes and prediabetes. Our findings further highlight that individuals with concurrent fat accumulation in both organs face a markedly higher risk than those with fat in either the liver or pancreas alone. These findings underscore the critical role of specific fat distribution patterns in the pathogenesis of diabetes, which may inform future preventive and therapeutic strategies.

Availability of data and materials

All the data generated or analyzed during this study are available from the corresponding author upon reasonable request.

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Ethical approval

Ethics approval was obtained from the Gongli Hospital of Shanghai Pudong New Area. The study was conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived by the Ethics Committee of Gongli Hospital of Shanghai Pudong New Area because of the retrospective nature of the study.

Conflict of interest

The authors declare no conflict of interest.

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