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Associations of Intrapancreatic Fat Deposition With Incident Diseases of the Exocrine and Endocrine Pancreas: A UK Biobank Prospective Cohort Study

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INTRODUCTION: To investigate whether increased intrapancreatic fat deposition (IPFD) heightens the risk of diseases of the exocrine and endocrine pancreas.

METHODS: A prospective cohort study was conducted using data from the UK Biobank. IPFD was quantified using MRI and a deep learning–based framework called nnUNet. The prevalence of fatty change of the pancreas (FP) was determined using sex- and age-specific thresholds. Associations between IPFD and pancreatic diseases were assessed with multivariate Cox-proportional hazard model adjusted for age, sex, ethnicity, body mass index, smoking and drinking status, central obesity, hypertension, dyslipidemia, liver fat content, and spleen fat content.

RESULTS: Of the 42,599 participants included in the analysis, the prevalence of FP was 17.86%. Elevated IPFD levels were associated with an increased risk of acute pancreatitis (hazard ratio [HR] per 1 quintile change 1.513, 95% confidence interval [CI] 1.179–1.941), pancreatic cancer (HR per 1 quintile change 1.365, 95% CI 1.058–1.762) and diabetes mellitus (HR per 1 quintile change 1.221, 95% CI 1.132–1.318). FP was also associated with a higher risk of acute pancreatitis (HR 3.982, 95% CI 2.192–7.234), pancreatic cancer (HR 1.976, 95% CI 1.054–3.704), and diabetes mellitus (HR 1.337, 95% CI 1.122–1.593, $P = 0.001$).

DISCUSSION: FP is a common pancreatic disorder. Fat in the pancreas is an independent risk factor for diseases of both the exocrine pancreas and endocrine pancreas.

KEYWORDS: intrapancreatic fat deposition; fatty change of the pancreas; acute pancreatitis; pancreatic cancer; diabetes mellitus

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/D240>.

Am J Gastroenterol 2024;119:1158–1166. <https://doi.org/10.14309/ajg.0000000000002792>

INTRODUCTION

Intrapancreatic fat deposition (IPFD) is the diffuse presence of fat within the pancreas (1). In contrast to the liver, which stores fat exclusively in lipid droplets within liver cells, IPFD involves a variety of cells, including endocrine cells, acinar cells, adipocytes, and others (2,3). IPFD can occur through either lipid droplet accumulation inside cells or the substitution of functional cells with adipocytes.

Although a small amount of fat usually exists in the pancreas of healthy individuals, excessive IPFD leads to fatty change of the pancreas (FP) (4). The prevalence of FP varies greatly between published studies, ranging from 8.4% to 35.0% (5–9); 1 reason for this might be the retrospective analyses of imaging databases that collect data from large tertiary referral centers, which may not represent the general population and involve various noninvasive imaging techniques such

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Received December 14, 2023; accepted March 19, 2024; published online April 8, 2024

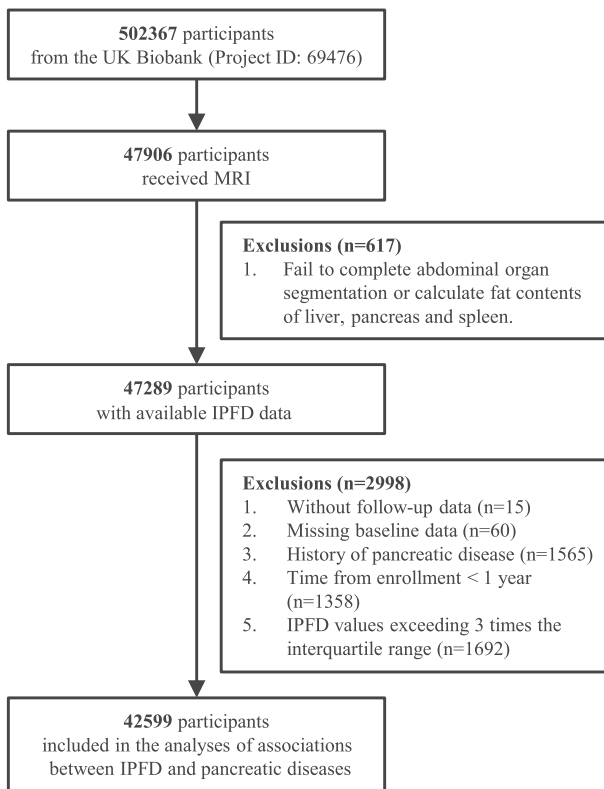


Figure 1. Flowchart of the study. IPFD, intrapancreatic fat deposition; MRI, magnetic resonance imaging.

as ultrasonography, endoscopic ultrasound, computed tomography, and magnetic resonance imaging (MRI).

FP, or excessive IPFD, may disrupt normal pancreatic function and elevate the risk of diabetes mellitus (DM), acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC) (10–13). Many studies have focused on the association between FP and DM; however, results are still inconsistent, possibly because of small sample sizes, population differences, and lack of standardized imaging detection methods (14–17). In addition, fewer studies have explored an association between FP and AP, CP, or PC, and the available studies were all cross-sectional and case-control studies (10,12,18,19). There was a lack of a standardized diagnosis definition, using unified detection methods, and large-scale cohort studies conducted in the general

population. The advancement of chemical shift MRI technology has enabled quantitative evaluation of fat content in tissues, thereby mitigating the impact of incomplete diagnostic criteria for FP (14,20). The large-scale, prospective cohort of the UK Biobank and standardized chemical shift MRI examinations provide an opportunity for further exploration into the above-mentioned issues.

In this study, we initially conducted a prospective cohort study involving a population from the UK Biobank to investigate the prevalence of FP, then explored the association between IPFD and the occurrence of pancreatic diseases.

METHODS

Study design and participants

The UK Biobank is a large database of more than 500,000 participants recruited from the general population (21). In this database, 47,906 participants underwent an abdominal Dixon MRI from July 2014 to January 2023, and the level of IPFD was calculated. A prospective cohort study was conducted in this research. Outcomes were diseases of the exocrine and endocrine pancreas (including AP, PC, DM, and other pancreatic diseases). Exposure was determined by IPFD level. Covariates included variables such as age, sex, ethnicity, body mass index (BMI), waist circumference, hip circumference, Townsend deprivation index, smoking status, alcohol consumption, and disease history. Participants were excluded when any of the following criteria were met: (i) without follow-up data; (ii) missing baseline data; (iii) history of pancreatic disease; (iv) time from enrollment <1 year; and (v) IPFD values exceeding 3 times the interquartile range. In our study, we used the MRI examination time point (the time of IPFD measurement) as the baseline. However, for some participants, certain variables such as Townsend deprivation index, smoking, and drinking status were missing during the MRI examination. In such cases, we used data recorded before the MRI examination (information collected at initial registration of the participant into the UK Biobank) to fill in these missing values. Subsequently, participants who still had missing data were excluded from the analysis. After exclusion, 42,599 eligible participants were included for further analysis (Figure 1). This study was approved by the North West Multi-Centre Research Ethics Committee, with all participants providing written informed consent. This study was additionally reviewed and approved by the UK Biobank (Project ID: 69476). Baseline characteristics of participants with available IPFD data were generally comparable with that of other participants (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/AJG/D240>).

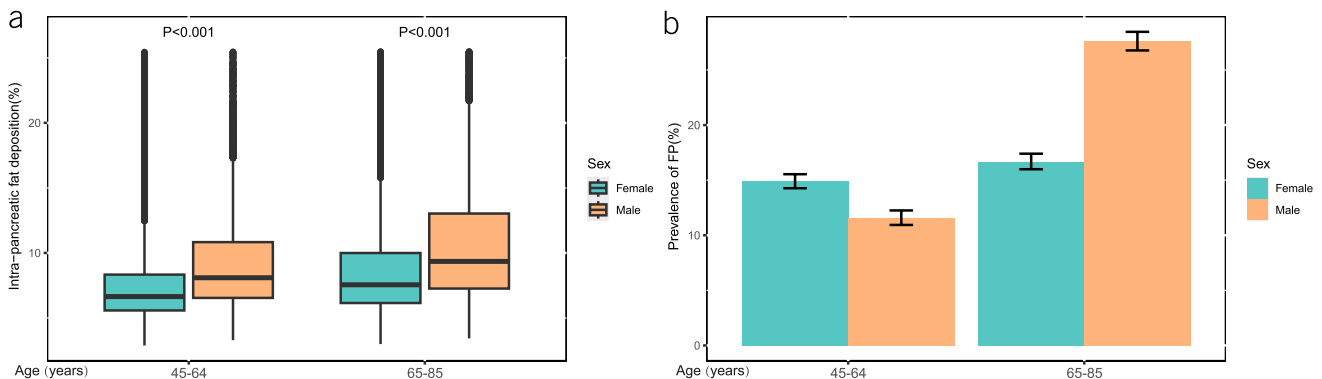


Figure 2. Distribution of IPFD (a) and the prevalence of FP (b) by sex and age. The boxes represented medians with interquartile ranges (a) or proportions (b). The whiskers represented $1.5 \times$ interquartile ranges (a) or confidence interval (b). FP, fatty change of the pancreas; IPFD, intrapancreatic fat deposition.

Measurement of intrapancreatic fat and fat content of liver and spleen

The measurement of IPFD and fat content in the liver and spleen involved 2 steps. Initially, we performed organ segmentation using an organ autosegmentation model based on nnUNet (22). nnUNet is a deep learning–based image segmentation framework developed by Isensee Fabian et al at the German Research Center (23). Owing to its high performance and ease of use, nnUNet has been widely used in medical image segmentation tasks, such as tumor segmentation, left ventricular segmentation of the heart, and neuronal segmentation. The model used for this study was trained by Kart Turkay et al with MRIs from the UK Biobank. Mean Dice scores (a quantitative evaluation method of accuracy)

of the model compared with manual reference segmentations were 0.971, 0.946, and 0.83 for the liver, spleen, and pancreas (22). After organ segmentation, the fat content of the pancreas and liver was calculated using the following formula: fat/(fat + water) $\times$ 100%. The fat and water images were reconstructed from the in-phase and out-of-phase images obtained from the 2-point Dixon acquisition. The resultant fat fraction values were calculated for each voxel within the organ masks predicted by the nnUNet model. To eliminate any abnormal hyperintensity resulting from the partial volume effect, caused by relatively thick slices, the outermost pixel layer at the organ boundary was removed (24). Finally, we calculated the mean value across the whole organ.

Table 1. Baseline characteristics of participants grouped by quintiles of IPFD

	All (N = 42,599)	Quintiles of IPFD					P value
		Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Follow-up time (yr)	4.61 (3.77 to 5.98)	4.6 (3.77 to 5.84)	4.66 (3.81 to 6.11)	4.68 (3.81 to 6.06)	4.63 (3.77 to 6)	4.52 (3.67 to 5.84)	<0.001
Age	65 (58 to 70)	61 (56 to 68)	63 (57 to 69)	65 (58 to 70)	66 (60 to 71)	67 (61 to 72)	<0.001
Sex (male)	19,855 (46.61)	2,232 (26.2)	3,265 (38.32)	4,074 (47.82)	4,811 (56.47)	5,473 (64.24)	<0.001
Ethnicity (White)	39,285 (92.22)	7,781 (91.34)	7,793 (91.47)	7,823 (91.83)	7,917 (92.92)	7,970 (93.54)	<0.001
BMI	25.73 (23.41 to 28.54)	23.17 (21.54 to 25.15)	24.62 (22.79 to 26.8)	25.83 (23.81 to 28.21)	27.11 (24.89 to 29.75)	28.39 (25.99 to 31.28)	<0.001
Waist circumference	87 (79 to 96)	77.5 (72 to 84)	83 (76 to 90)	88 (80 to 94)	92 (85 to 99)	96 (89 to 103)	<0.001
Hip circumference	100 (95 to 105)	96 (92 to 100)	98 (94 to 103)	100 (95 to 105)	101 (97 to 107)	103 (99 to 109)	<0.001
Central obesity	29,240 (68.64)	3,136 (36.81)	4,943 (58.02)	6,179 (72.53)	7,138 (83.78)	7,844 (92.07)	<0.001
TDI	−2.61 (−3.88 to −0.5)	−2.57 (−3.9 to −0.48)	−2.61 (−3.92 to −0.46)	−2.59 (−3.85 to −0.45)	−2.63 (−3.9 to −0.52)	−2.63 (−3.83 to −0.59)	0.540
Tobacco smoking							<0.001
Never	26,694 (62.66)	5,880 (69.02)	5,588 (65.59)	5,302 (62.24)	5,068 (59.48)	4,855 (56.98)	
Previous	14,442 (33.9)	2,420 (28.41)	2,645 (31.04)	2,915 (34.22)	3,089 (36.26)	3,373 (39.59)	
Current	1,463 (3.43)	219 (2.57)	287 (3.37)	302 (3.55)	363 (4.26)	292 (3.43)	
Heavy alcohol consumption							0.286
Never	1,336 (3.14)	284 (3.33)	267 (3.13)	263 (3.09)	249 (2.92)	273 (3.2)	
Previous	1,378 (3.23)	308 (3.62)	259 (3.04)	276 (3.24)	282 (3.31)	253 (2.97)	
Current	39,885 (93.63)	7,927 (93.05)	7,994 (93.83)	7,980 (93.67)	7,989 (93.77)	7,994 (93.83)	
Hypertension	5,609 (13.17)	541 (6.35)	776 (9.11)	1,116 (13.1)	1,397 (16.4)	1,779 (20.88)	<0.001
Dyslipidemia	2,604 (6.11)	221 (2.59)	334 (3.92)	506 (5.94)	662 (7.77)	881 (10.34)	<0.001
History of gallstones	1,537 (3.61)	187 (2.2)	229 (2.69)	302 (3.55)	364 (4.27)	455 (5.34)	<0.001
Lipid-lowering drugs	3,239 (7.6)	565 (6.63)	605 (7.1)	619 (7.27)	707 (8.3)	743 (8.72)	<0.001
Glucose-lowering drugs	589 (1.38)	33 (0.39)	61 (0.72)	109 (1.28)	157 (1.84)	229 (2.69)	<0.001
IPFD (%)	7.72 (6.22 to 10.5)	5.28 (4.8 to 5.63)	6.5 (6.22 to 6.78)	7.72 (7.39 to 8.11)	9.7 (9.07 to 10.5)	14.97 (12.91 to 18.3)	<0.001
Liver fat content (%)	4.79 (4.32 to 5.96)	4.3 (4.01 to 4.68)	4.55 (4.21 to 5.05)	4.81 (4.38 to 5.7)	5.25 (4.62 to 6.86)	5.95 (4.85 to 8.67)	<0.001
Spleen fat content (%)	5.45 (4.85 to 6.5)	4.9 (4.52 to 5.43)	5.21 (4.75 to 5.85)	5.5 (4.93 to 6.47)	5.89 (5.14 to 7.18)	6.22 (5.32 to 7.99)	<0.001
Pancreatic disease	782 (1.84)	56 (0.66)	73 (0.86)	140 (1.64)	173 (2.03)	340 (3.99)	<0.001
Exocrine disease	143 (0.34)	17 (0.2)	17 (0.2)	26 (0.31)	25 (0.29)	58 (0.68)	<0.001
Acute pancreatitis	55 (0.13)	7 (0.08)	7 (0.08)	8 (0.09)	6 (0.07)	27 (0.32)	<0.001
Pancreatic cancer	52 (0.12)	4 (0.05)	6 (0.07)	11 (0.13)	7 (0.08)	24 (0.28)	<0.001
Other	65 (0.15)	7 (0.08)	9 (0.11)	12 (0.14)	14 (0.16)	23 (0.27)	0.018
Endocrine disease	659 (1.55)	42 (0.49)	56 (0.66)	118 (1.39)	151 (1.77)	292 (3.43)	<0.001
Diabetes mellitus	636 (1.49)	36 (0.42)	51 (0.6)	113 (1.33)	149 (1.75)	287 (3.37)	<0.001
Other	38 (0.09)	9 (0.11)	5 (0.06)	9 (0.11)	4 (0.05)	11 (0.13)	0.327

Continuous values were presented as median (interquartile range), and categorical variables were presented as counts (percentages). BMI, body mass index; IPFD, intrapancreatic fat deposition; TDI, Townsend deprivation index.

Diagnosis and definition

All diseases were diagnosed based on the *International Classification of Diseases, Ninth and Tenth Revisions* with specific coding detailed in Supplementary Table 2 (see Supplementary Digital Content 1, <http://links.lww.com/AJG/D240>). According to the division of age limited by World Health Organization, individuals were categorized as middle-aged (younger than 65 years) and elderly (aged 65 years and older). Central obesity was defined as meeting one of the following criteria: for males, waist circumference ≥ 90 cm or waist-to-hip ratio ≥ 0.9 , or waist-to-height ratio ≥ 0.5 , and for females, waist circumference ≥ 80 cm or waist-to-hip ratio ≥ 0.85 , or waist-to-height ratio ≥ 0.5 . Lipid-lowering and glucose-lowering drugs were presented in Supplementary Table 3 (see Supplementary Digital Content 1, <http://links.lww.com/AJG/D240>). The determination of FP was derived from the sex- and age-specific 95th percentile upper limit of IPFD in the general population (25–27). After excluding participants with a BMI of 25 or higher, central obesity, current or past histories of smoking and alcohol intake, hypertension, and lipid metabolism disorders, 8.01% for females aged 45–54 years, 11.03% for females aged 55–64 years, 11.70% for females aged 65 years and older, 11.96% for males aged 45–54 years, 15.77% for males aged 55–64 years, and 12.43% for males aged 65 years and older were used as the standard upper limit values for IPFD.

Statistical analysis

Continuous variables that conform to a normal distribution were presented as mean $\pm$ SD. Intergroup comparisons of normally distributed data involved using *t* tests for 2 groups or 1-way ANOVA for multiple groups. Non-normally distributed data were represented by the median (quartile range) (M (P25, P75)), and the Mann–Whitney *U* test or Kruskal–Wallis *H* test was used for intergroup comparison. Categorical variables were analyzed using the χ^2 test, with the Fisher exact test used when deemed necessary. Standard differences in baseline data were assessed between individuals who underwent MRI examinations and those who did not.

Associations of IPFD with pancreatic diseases (including DM, AP, and PC) were investigated using Cox-proportional hazard models. Quintiles for IPFD and FP based on sex- and age-specific 95th percentile normal upper limit of IPFD were derived, and hazard ratios (HRs) were calculated. For the survival analysis, the Kaplan–Meier method was used to estimate the cumulative hazard. Three incremental models were developed, wherein each model included more covariates than the previous one. Model 0 was a univariate model, whereas model 1 adjusted for age, sex, ethnicity, BMI, smoking status (current, former, and never), drinking status (current, former, and never), and central obesity. Model 2 was further adjusted for hypertension, dyslipidemia, liver fat content, and spleen fat content. Subgroup analyses were conducted to assess associations between IPFD and pancreatic diseases, grouping participants according to age (middle-aged and elderly), sex, BMI (underweight/normal, overweight, and obesity), smoking status, drinking status, central obesity, history of gallstones, and history of lipid-lowering and glucose-lowering drugs, adjusting for the covariates in model 2 when appropriate.

A sensitivity analysis was conducted to assess the robustness of the results, including participants who had IPFD values exceeding 3 times the interquartile range as outliers.

All analyses were performed using R software version 4.2.2 and GraphPad Prism 8.0.2. A 2-sided *P* value of ≤ 0.05 was designated statistically significant.

RESULTS

Characteristics of the study population

After the initial exclusion step, 42,599 eligible participants were included for further analysis (Figure 1). Of these, 7,607 (17.86%) participants had FP according to the sex- and age-specific 95th percentile upper limit of IPFD in healthy participants. Figure 2 presents comparisons of IPFD and the prevalence of FP between sexes and ages. A trend of increasing FP prevalence was observed with advanced age in both males and females (see Supplementary Table 4, Supplementary Digital Content 1, <http://links.lww.com/AJG/D240>). The

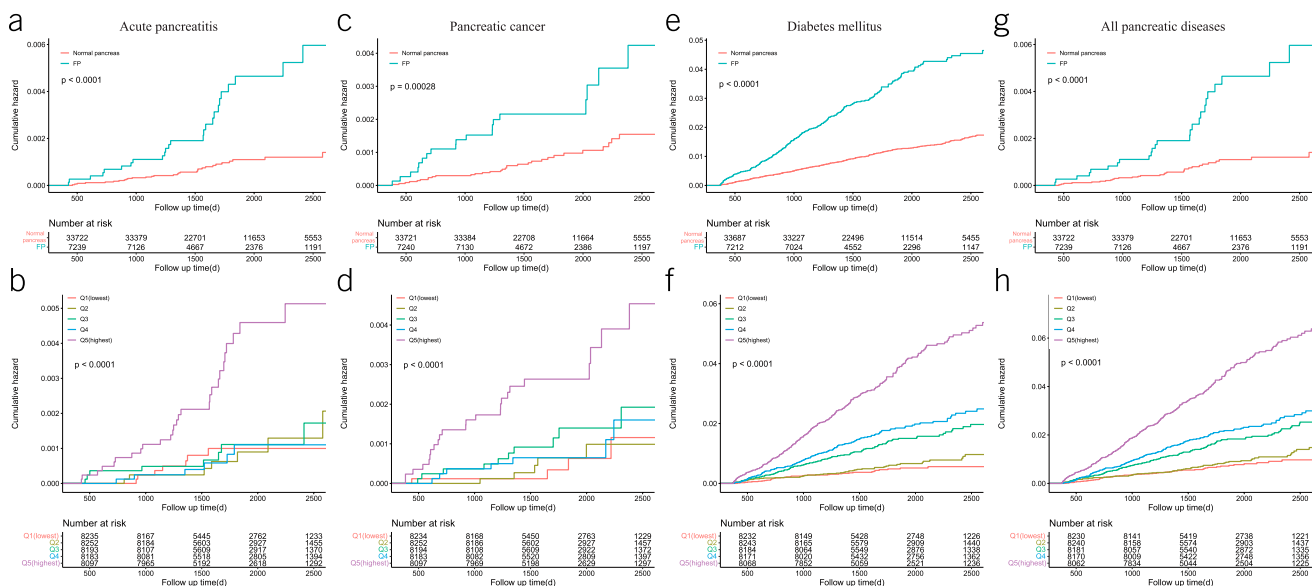


Figure 3. Kaplan-Meier estimates of acute pancreatitis (a, b), pancreatic cancer (c, d), diabetes mellitus (e, f), and all pancreatic diseases (g, h). FP, fatty change of the pancreas.

baseline characteristics of participants grouped by quintiles of IPFD or FP were summarized in Tables 1 and 2.

Associations of IPFD with pancreatic diseases

Of the 42,599 participants, 782 (1.84%) had new-onset pancreatic disease over a medium follow-up period of 4.61 years (interquartile range 3.77–5.98 years), including 55 (0.13%) with AP, 52 (0.12%) with PC, 65 (0.15%) with other exocrine diseases, 636 (1.49%) with DM, and 38 (0.09%) with other endocrine diseases (Table 1). Participants with higher IPFD levels had an elevated cumulative risk of developing pancreatic diseases (Table 3 and Figure 3). After adjusting for possible confounding factors, a clear relationship was found between IPFD level and the incidence of AP (HR 1.513, 95% confidence interval [CI] 1.179–1.941, $P = 0.001$), PC (HR 1.365, 95% CI 1.058–1.762, $P = 0.017$), DM (HR 1.221, 95% CI 1.132–1.318, $P < 0.001$), and all pancreatic diseases (HR 1.227, 95% CI 1.147–1.313, $P < 0.001$) (Figure 4 and see Supplementary Table 4, Supplementary Digital Content 1, <http://links.lww.com/AJG/D240>). FP was also associated with a higher risk of AP (HR 3.982, 95% CI

2.192–7.234, $P < 0.001$), PC (HR 1.976, 95% CI 1.054–3.704, $P = 0.034$), DM (HR 1.337, 95% CI 1.122–1.593, $P = 0.001$), and all pancreatic diseases (HR 1.441, 95% CI 1.228–1.692, $P < 0.001$) (see Supplementary Table 5, Supplementary Digital Content 1, <http://links.lww.com/AJG/D240>).

Subgroup and sensitivity analyses

Subgroup analyses were conducted according to age, sex, BMI, central obesity, smoking and drinking status, history of gallstones, and the use of lipid-lowering or glucose-lowering drugs (Figure 5). Compared with participants with central obesity, IPFD had a higher HR for AP in participants without central obesity (P for interaction = 0.006). There was no interaction between a history of gallstones and IPFD in relation to any specific pancreatic disease; however, it had a significant interaction with all pancreatic diseases. In the sensitivity analysis, the results remained consistent for AP and DM but exhibited instability for PC (see Supplementary Table 6, Supplementary Digital Content 1, <http://links.lww.com/AJG/D240>).

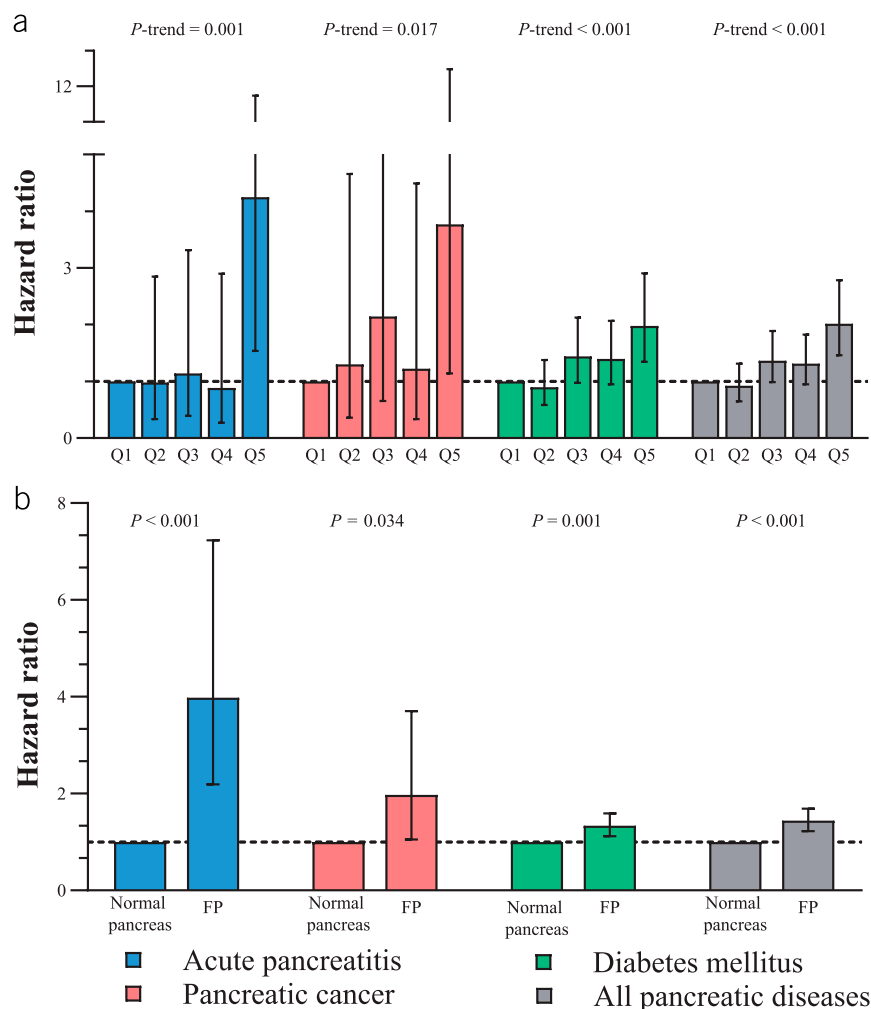


Figure 4. Cox regression model of the association between IPFD and all pancreatic diseases, DM, AP, and PC. (a) Participants were grouped by IPFD quintiles. Q1–Q5 represented the quintiles of IPFD, and individuals in the lowest quintile of IPFD (Q1) were used as the reference group. (b) Participants were grouped by FP diagnosis. Data presented as hazard ratio (95% CI), adjusted with model 2 for age, sex, ethnicity, BMI, central obesity, smoking and drinking status, hypertension, dyslipidemia, liver fat content, and spleen fat content. AP, acute pancreatitis; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FP, fatty change of the pancreas; IPFD, intrapancreatic fat deposition; PC, pancreatic cancer.

DISCUSSION

This is currently the largest prospective, population-based study on clinical relationships of increased IPFD. The prevalence of FP was 17.86% in a population of 42,599 participants from the UK Biobank, a database collection from the general population. Fat in the pancreas was significantly associated with the development of new-onset diseases of the exocrine and endocrine pancreas.

The strength of this study lies in the inclusion of participants with the largest reported sample size from a general population. The follow-up period of at least 1 year minimizes the probability of reverse causation. In addition, we used a deep learning-based method of abdominal organ segmentation (nnUNet) to automatically calculate the average IPFD for the entire pancreas. In previous studies, the measurement of IPFD was often performed by manually delineating regions of interest on imaging scans and calculating the average IPFD within these regions. However, this region of interest-based approach has its limitations because it may introduce selection bias and may not fully reflect overall changes in the pancreas. In addition, this method relies heavily on manual operations, making it challenging to apply in large-scale studies. By contrast, the use of nnUNet, a deep learning-based tool, offers several advantages for measuring IPFD. First, it allows for automated segmentation of the pancreas, minimizing the potential bias introduced by manual delineation. Second, nnUNet has demonstrated high accuracy in segmentation tasks and has been widely adopted in various research fields (28–30). Moreover, nnUNet is a versatile and adaptable tool that does not require manual task-specific adaptation, making it more convenient for application in different cohorts (23). With the increasing availability of high-quality clinical research data, AI tools based on deep learning, such as nnUNet, have the potential to facilitate efficient and accurate measurements of IPFD in large-scale studies.

Considering the distinct sex differences in IPFD, we used sex- and age-specific upper limit of normal, resulting in an FP prevalence of 17.86%. To date, only a few studies have reported the distribution of IPFD and the prevalence of FP in the general population. The most reliable data were from MRI examinations of 685 Hong Kong

adults (27), using the 95th percentile of IPFD in healthy individuals as the upper limit of normal, with an FP prevalence of 16.1%, similar to our results. In the same age group, males have higher levels of IPFD. When using sex- and age-specific thresholds as diagnostic criteria, both sexes show an increasing trend with age. In another meta-analysis covering 11 cohorts (including 12,675 individuals), the prevalence of FP in populations with various metabolic disorders can reach 33%. With the increasing prevalence of metabolic disorders such as obesity and dyslipidemia, the incidence rate of FP may also gradually increase (31).

Regarding the association between IPFD and the incidence of pancreatic diseases, there are some interesting findings. Our study was the first prospective longitudinal cohort to investigate the association between increased IPFD and risk of AP in the general population. Although previous limited cross-sectional and case-control studies have shown this association, there has been a lack of prospective cohort studies to support it (11,19,32). Our study filled this gap and provided strong evidence. This study also found a consistent association between elevated IPFD and an increased risk of DM, consistent with previous studies (9,13,16,17). Our study added to existing literature by confirming the association between IPFD and DM in a larger sample cohort. With regard to PC, we found a significant correlation between IPFD and PC, whether grouped by IPFD quintiles or FP (12,33). However, the results were also found to be unstable in the sensitivity analysis. Our study excluded participants with a history of acute and CP and those who had a relatively short follow-up time. This resulted in a small number of cases, which may be the reason for the unstable results. For CP, studies have reported the relationship between IPFD and its incidence, but our study did not analyze these individuals separately owing to the small number of participants with CP (10,34). Overall, the above findings provide a strong support for the PANcreatic Diseases Originating from intrRa-pancreatic fAt (PANDORA) hypothesis, which postulates that increased IPFD is the single most important driver for diseases of both the exocrine pancreas and the endocrine pancreas (4).

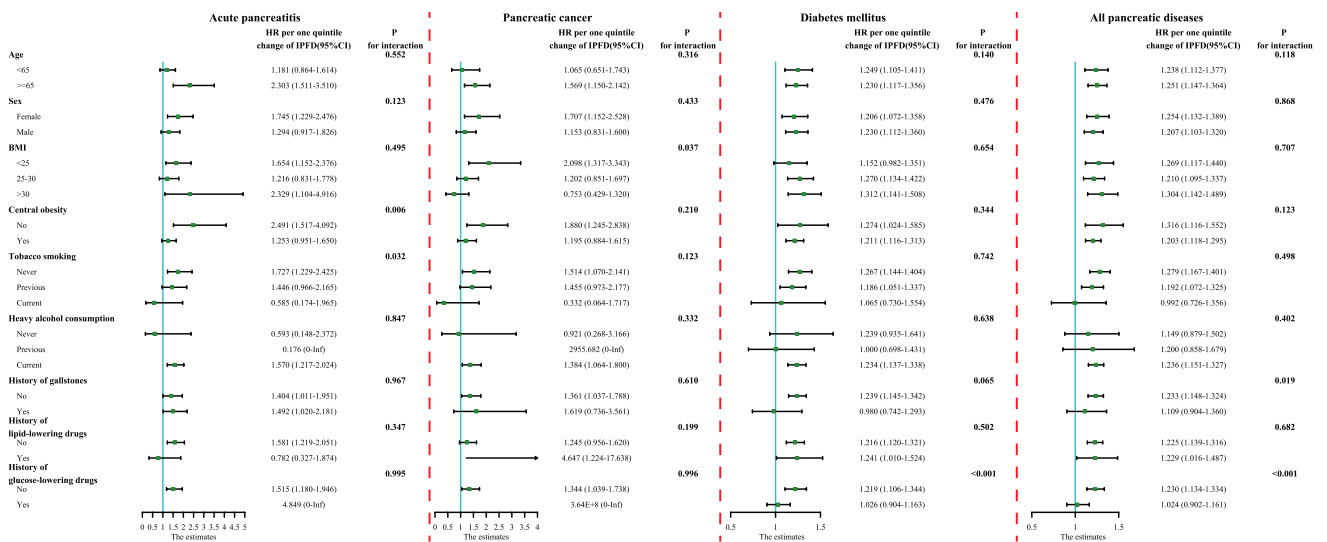


Figure 5. Subgroup analysis for the association between IPFD and AP, PC, DM, and all pancreatic diseases. Data presented as hazard ratio (95% CI), adjusted with model 2 for age, sex, ethnicity, BMI, central obesity, smoking and drinking status, hypertension, dyslipidemia, liver fat content, and spleen fat content. AP, acute pancreatitis; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FP, fatty fat content of the pancreas; PC, pancreatic cancer.

Table 2. Baseline characteristics of participants grouped by the presence or absence of FP

	All (N = 42,599)	FP		P value
		No (n = 34,992)	Yes (n = 7,607)	
Follow-up time (yr)	4.61 (3.77 to 5.98)	4.64 (3.79 to 5.99)	4.53 (3.68 to 5.91)	<0.001
Age	65 (58 to 70)	64 (58 to 70)	67 (60 to 72)	<0.001
Sex (male)	19,855 (46.61)	15,828 (45.23)	4,027 (52.94)	<0.001
Ethnicity (White)	39,285 (92.22)	32,170 (91.94)	7,115 (93.53)	<0.001
BMI	25.73 (23.41 to 28.54)	25.2 (23.03 to 27.76)	28.53 (26.05 to 31.57)	<0.001
Waist circumference	87 (79 to 96)	86 (77 to 93)	96 (88 to 103)	<0.001
Hip circumference	100 (95 to 105)	99 (94 to 104)	104 (99 to 110)	<0.001
Central obesity	29,240 (68.64)	22,293 (63.71)	6,947 (91.32)	<0.001
TDI	−2.61 (−3.88 to −0.5)	−2.62 (−3.9 to −0.49)	−2.59 (−3.8 to −0.53)	0.053
Tobacco smoking				<0.001
Never	26,694 (62.66)	22,302 (63.73)	4,392 (57.74)	
Previous	14,442 (33.9)	11,486 (32.82)	2,956 (38.86)	
Current	1,463 (3.43)	1,204 (3.44)	259 (3.4)	
Heavy alcohol consumption				0.051
Never	1,336 (3.14)	1,069 (3.05)	267 (3.51)	
Previous	1,378 (3.23)	1,151 (3.29)	227 (2.98)	
Current	39,885 (93.63)	32,772 (93.66)	7,113 (93.51)	
Hypertension	5,609 (13.17)	4,058 (11.6)	1,551 (20.39)	<0.001
Dyslipidemia	2,604 (6.11)	1,872 (5.35)	732 (9.62)	<0.001
History of gallstones	1,537 (3.61)	1,092 (3.12)	445 (5.85)	<0.001
Lipid-lowering drugs	3,239 (7.6)	2,570 (7.34)	669 (8.79)	<0.001
Glucose-lowering drugs	589 (1.38)	388 (1.11)	201 (2.64)	<0.001
IPFD (%)	7.72 (6.22 to 10.5)	7.14 (5.97 to 8.75)	15.48 (13.11 to 18.78)	<0.001
Liver fat content (%)	4.79 (4.32 to 5.96)	4.68 (4.26 to 5.51)	5.86 (4.81 to 8.6)	<0.001
Spleen fat content (%)	5.45 (4.85 to 6.5)	5.34 (4.79 to 6.24)	6.2 (5.3 to 7.95)	<0.001
Pancreatic disease	782 (1.84)	499 (1.43)	283 (3.72)	<0.001
Exocrine disease	143 (0.34)	92 (0.26)	51 (0.67)	<0.001
Acute pancreatitis	55 (0.13)	30 (0.09)	25 (0.33)	<0.001
Pancreatic cancer	52 (0.12)	33 (0.09)	19 (0.25)	<0.001
Other	65 (0.15)	47 (0.13)	18 (0.24)	0.056
Endocrine disease	659 (1.55)	417 (1.19)	242 (3.18)	<0.001
Diabetes mellitus	636 (1.49)	399 (1.14)	237 (3.12)	<0.001
Other	38 (0.09)	29 (0.08)	9 (0.12)	0.468

Continuous values were presented as median (interquartile range), and categorical variables were presented as counts (percentages). BMI, body mass index; FP, fatty change of the pancreas; IPFD, intrapancreatic fat deposition; TDI, Townsend deprivation index.

There were several limitations in this study. First, the UK Biobank database, in itself, has certain limitations, including a limited response rate to recruitment invitations (approximately 5%), which may introduce potential self-selection bias among the study participants. It is important to acknowledge that most participants who were enrolled were predominantly white and older than 45 years. Further studies on clinical relationships of increased IPFD with pancreatic diseases should be conducted in populations of different ages and ethnicities to gain a more comprehensive understanding of its distribution in the population. In addition, ICD

codes were used for diagnosis; however, they were primarily designed for billing and administrative purposes and may be subject to miscoding because of human error. Second, the median follow-up time in this study was only 4.61 years (interquartile range 3.77–5.98 years), which may not be sufficient to fully demonstrate the impact of IPFD. Thirdly, the IPFD data in this study were based on a single time point. One study showed that short-term training can effectively reduce ectopic fat in the pancreas and exercise training may therefore reduce the risk of type 2 diabetes (35). Fortunately, the UK Biobank is a long-term follow-up population

Table 3. Incidence density of diseases of the pancreas according to fat in the pancreas

	Acute pancreatitis		Pancreatic cancer		Diabetes mellitus		All pancreatic diseases	
	Event	Incidence density (per 1,000 person-years)	Event	Incidence density (per 1,000 person-years)	Event	Incidence density (per 1,000 person-years)	Event	Incidence density (per 1,000 person-years)
All (n = 42,599)	55	0.263 (0.193–0.332)	52	0.248 (0.181–0.316)	636	3.057 (2.820–3.294)	782	3.764 (3.500–4.027)
Quintiles of IPFD								
Q1 (lowest) (n = 8,520)	7	0.168 (0.043–0.292)	4	0.096 (0.002–0.190)	36	0.864 (0.582–1.146)	56	1.345 (0.993–1.697)
Q2	7	0.164 (0.043–0.286)	6	0.141 (0.028–0.254)	51	1.200 (0.871–1.530)	73	1.720 (1.326–2.114)
Q3	8	0.189 (0.058–0.320)	11	0.260 (0.106–0.414)	113	2.689 (2.194–3.184)	140	3.334 (2.782–3.885)
Q4	6	0.143 (0.029–0.257)	7	0.167 (0.043–0.290)	149	3.581 (3.007–4.155)	173	4.163 (3.544–4.782)
Q5 (highest)	27	0.661 (0.412–0.911)	24	0.587 (0.352–0.822)	287	7.132 (6.310–7.954)	340	8.469 (7.573–9.365)
FP								
No (n = 34,992)	30	0.174 (0.112–0.236)	33	0.191 (0.126–0.256)	399	2.321 (2.094–2.549)	499	2.906 (2.652–3.161)
Yes (n = 7,607)	25	0.682 (0.415–0.949)	19	0.518 (0.285–0.751)	237	6.554 (5.722–7.386)	283	7.844 (6.934–8.754)

FP, fatty change of the pancreas; IPFD, intrapancreatic fat deposition.

cohort with continuously updated data, and a second follow-up for abdominal MRI is underway. Further research can help address the aforementioned second and third points to some extent. In addition, there is another limitation to this study, which used an average fat fraction for the entire pancreas, and this could have ignored any degree of spatial heterogeneity. However, a large MRI cohort at 3 T showed that there were actually no regional differences in the pancreas in terms of IPFD, when demographics, body composition, and other possible confounders were taken into account (36).

In conclusion, we report the prevalence of FP in a large, population-based cohort and identified elevated IPFD and FP as significant risk factors for AP, PC, and DM. Purposely designed studies are now warranted to investigate the pathogenic mechanisms of FP to reduce its incidence and mitigate its impact on diseases of the exocrine and endocrine pancreas.

ACKNOWLEDGMENTS

We thank the participants of the UK Biobank.

CONFLICTS OF INTEREST

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conceptualization. X.M., X.S., and W.C.: methodology. X.D. and Y.W.: formal analysis. X.D., Q.Z., and C.Y.: investigation. X.S. and Z.D.: data curation. X.D., L.C., and Q.S.: writing—original draft. G.L., W.L., and S.W.: writing—review and editing. Y.D., W.G., and W.X.: supervision. X.D., C.Y., X.S., Y.D., and G.L.: funding acquisition. G.L.: resources. All authors read and approved the final draft and took full responsibility for its content, including the accuracy of the data and its statistical analysis.

Financial support: This work was supported by the National Natural Science Foundation of China (No. 82200680, 82200720, 82200721, 82200996, 82241043, and 82173616); Cultivation Foundation of Yangzhou Municipal Key Laboratory (No. YZ2021147); The Medical Research Project of Jiangsu Provincial Health Commission (No. ZD2022011); Yangzhou key research and development plan (No.

YZ2022080); and Suzhou Innovation Platform Construction Projects-Municipal Key Laboratory Construction (No. SZS2023001).

Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Increased intrapancreatic fat deposition (IPFD) is common in general population.
- ✓ There is a paucity of longitudinal cohort studies investigating the relationship between fatty change of the pancreas (FP) and acute pancreatitis (AP), pancreatic cancer (PC), and diabetes mellitus (DM).

WHAT IS NEW HERE

- ✓ Prevalence of FP in the large population-based cohort was 17.86%.
- ✓ Increasing IPFD by 1 quintile raised the risk of AP by 51.3%, PC by 36.5%, and DM by 22.1%.
- ✓ FP independently increased the risks of AP by 298.2%, PC by 97.6%, and DM by 33.7%.

REFERENCES

- Petrov MS, Taylor R. Intra-pancreatic fat deposition: Bringing hidden fat to the fore. *Nat Rev Gastroenterol Hepatol* 2022;19(3):153–68.
- Molnar L, Kerekes E, Meszaros A. Significance of the fatty infiltration of the pancreas [in Hungarian]. *Orv Hetil* 1958;99(36):1243–6.
- Tong X, Dai C, Walker JT, et al. Lipid droplet accumulation in human pancreatic islets is dependent on both donor age and health. *Diabetes* 2020;69(3):342–54.
- Petrov MS. Fatty change of the pancreas: The Pandora's box of pancreatology. *Lancet Gastroenterol Hepatol* 2023;8(7):671–82.
- Wang CY, Ou HY, Chen MF, et al. Enigmatic ectopic fat: Prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. *J Am Heart Assoc* 2014;3(1):e000297.
- Sepe PS, Ohri A, Sanaka S, et al. A prospective evaluation of fatty pancreas by using EUS. *Gastrointest Endosc* 2011;73(5):987–93.

7. Lesmana CR, Pakasi LS, Inggriani S, et al. Prevalence of non-alcoholic fatty pancreas disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: A large cross sectional study. *BMC Gastroenterol* 2015;15:174.
8. Koc U, Taydas O. Evaluation of pancreatic steatosis prevalence and anthropometric measurements using non-contrast computed tomography. *Turk J Gastroenterol* 2020;31(9):640–8.
9. Hung CS, Tseng PH, Tu CH, et al. Increased pancreatic echogenicity with US: Relationship to glycemic progression and incident diabetes. *Radiology* 2018;287(3):853–63.
10. Fujii M, Ohno Y, Yamada M, et al. Impact of fatty pancreas and lifestyle on the development of subclinical chronic pancreatitis in healthy people undergoing a medical checkup. *Environ Health Prev Med* 2019;24(1):10.
11. Ko J, Al-Ani Z, Long K, et al. Intrapaneatic, liver, and skeletal muscle fat depositions in first attack of acute pancreatitis versus health. *Am J Gastroenterol* 2022;117(10):1693–701.
12. Sreedhar UL, DeSouza SV, Park B, et al. A systematic review of intra-pancreatic fat deposition and pancreatic carcinogenesis. *J Gastrointest Surg* 2020;24(11):2560–9.
13. Yamazaki H, Tauchi S, Wang J, et al. Longitudinal association of fatty pancreas with the incidence of type-2 diabetes in lean individuals: A 6-year computed tomography-based cohort study. *J Gastroenterol* 2020;55(7):712–21.
14. Kuhn JP, Berthold F, Mayerle J, et al. Pancreatic steatosis demonstrated at MR imaging in the general population: Clinical relevance. *Radiology* 2015;276(1):129–36.
15. Yamazaki H, Tsuboya T, Katanuma A, et al. Lack of independent association between fatty pancreas and incidence of type 2 diabetes: 5-year Japanese cohort study. *Diabetes Care* 2016;39(10):1677–83.
16. Oh J, Park HJ, Lee ES, et al. Severity of hyperechoic pancreas on ultrasonography as a risk factor for glycemic progression. *Ultrasonography* 2021;40(4):499–511.
17. Chan TT, Tse YK, Lui RN, et al. Fatty pancreas is independently associated with subsequent diabetes mellitus development: A 10-year prospective cohort study. *Clin Gastroenterol Hepatol* 2022;20(9):2014–22.e4.
18. Ko J, Skudder-Hill L, Priya S, et al. Associations between intra-pancreatic fat deposition, pancreas size, and pancreatic enzymes in health and after an attack of acute pancreatitis. *Obes Facts* 2022;15(1):70–82.
19. Kromrey ML, Friedrich N, Hoffmann RT, et al. Pancreatic steatosis is associated with impaired exocrine pancreatic function. *Invest Radiol* 2019;54(7):403–8.
20. Kuhn JP, Hernando D, Munoz del Rio A, et al. Effect of multipeak spectral modeling of fat for liver iron and fat quantification: Correlation of biopsy with MR imaging results. *Radiology* 2012;265(1):133–42.
21. Collins R. What makes UK Biobank special? *Lancet* 2012;379(9822):1173–4.
22. Kart T, Fischer M, Kustner T, et al. Deep learning-based automated abdominal organ segmentation in the UK Biobank and German national cohort magnetic resonance imaging studies. *Invest Radiol* 2021;56(6):401–8.
23. Isensee F, Jaeger PF, Kohl SAA, et al. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. *Nat Methods* 2021;18(2):203–11.
24. Lin D, Wang Z, Li H, et al. Automated measurement of pancreatic fat deposition on Dixon MRI using nnU-Net. *J Magn Reson Imaging* 2023; 57(1):296–307.
25. Twig G, Yaniv G, Levine H, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med* 2016; 374(25):2430–40.
26. Harpavat S, Garcia-Prats JA, Anaya C, et al. Diagnostic yield of newborn screening for biliary atresia using direct or conjugated bilirubin measurements. *JAMA* 2020;323(12):1141–50.
27. Wong VW, Wong GL, Yeung DK, et al. Fatty pancreas, insulin resistance, and β -cell function: A population study using fat-water magnetic resonance imaging. *Am J Gastroenterol* 2014;109(4): 589–97.
28. Qu T, Li X, Wang X, et al. Transformer guided progressive fusion network for 3D pancreas and pancreatic mass segmentation. *Med Image Anal* 2023;86:102801.
29. OuYang PY, He Y, Guo JG, et al. Artificial intelligence aided precise detection of local recurrence on MRI for nasopharyngeal carcinoma: A multicenter cohort study. *EClinicalMedicine* 2023;63: 102202.
30. Hunter B, Chen M, Ratnakumar P, et al. A radiomics-based decision support tool improves lung cancer diagnosis in combination with the Herder score in large lung nodules. *EBioMedicine* 2022;86:104344.
31. Singh RG, Yoon HD, Wu LM, et al. Ectopic fat accumulation in the pancreas and its clinical relevance: A systematic review, meta-analysis, and meta-regression. *Metabolism* 2017;69:1–13.
32. Xie J, Xu L, Pan Y, et al. Nonalcoholic fatty pancreas disease is related independently to the severity of acute pancreatitis. *Eur J Gastroenterol Hepatol* 2019;31(8):973–8.
33. Rebours V, Gaujoux S, d'Assignies G, et al. Obesity and fatty pancreatic infiltration are risk factors for pancreatic precancerous lesions (PanIN). *Clin Cancer Res* 2015;21(15):3522–8.
34. Ko J, Stuart CE, Modesto AE, et al. Chronic pancreatitis is characterized by elevated circulating periostin levels related to intra-pancreatic fat deposition. *J Clin Med Res* 2020;12(9):568–78.
35. Heiskanen MA, Motiani KK, Mari A, et al. Exercise training decreases pancreatic fat content and improves beta cell function regardless of baseline glucose tolerance: A randomised controlled trial. *Diabetologia* 2018;61(8):1817–28.
36. Skudder-Hill L, Sequeira IR, Cho J, et al. Fat distribution within the pancreas according to diabetes status and insulin traits. *Diabetes* 2022; 71(6):1182–92.

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