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Estimating the effect of liver and pancreas volume and fat content on risk of diabetes: A Mendelian randomization study

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Abstract

Objective: Fat content and volume of liver and pancreas are associated with risk of diabetes in observational studies; whether these associations are causal is unknown. We conducted a Mendelian randomization (MR) study to examine causality of such associations.

Research design and methods: We used genetic variants associated ($p < 5\times10^{-8}$) with the exposures (liver and pancreas volume and fat content) using MRI scans of UK Biobank participants (n=32,859). We obtained summary-level data for risk of type 1 (9,358 cases) and type 2 (55,005 cases) diabetes from the largest available genome-wide association studies. We performed inverse-variance weighted MR as main analysis and several sensitivity analyses to assess pleiotropy and to exclude variants with potential pleiotropic effects.

Results: Observationally, liver fat and volume were associated with type 2 diabetes (odds ratio (OR) per one standard deviation (SD) higher exposure 2.16 [2.02 - 2.31] and 2.11 [1.96, 2.27], respectively). Pancreatic fat was associated with type 2 diabetes (1.42 [1.34, 1.51]) but not type 1 diabetes, and pancreas volume was negatively associated with type 1 diabetes (0.42 [0.36, 0.48]) and type 2 diabetes (0.73 [0.68, 0.78]). MR analysis provided evidence only for a causal role of liver fat and pancreas volume on risk of type 2 diabetes (1.27 [1.08,1.49] or 27% increased risk and 0.76 [0.62,0.94] or 24% decreased risk per 1SD, respectively) and no causal associations with type 1 diabetes.

Conclusions: Our findings assist in understanding the causal role of ectopic fat in the liver and pancreas and of organ volume in the pathophysiology of type 1 and 2 diabetes.

Introduction

The pancreas and the liver play key roles in the pathogenicity of both type 1 and type 2 diabetes in the context of beta cell dysfunction (1) and insulin resistance (2). Studies using autopsies, ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) have provided three main observations by comparing the levels of liver and pancreas fat deposition and volume between individuals with and without diabetes. First, individuals with type 1 (3) and type 2 diabetes (4) have smaller pancreases compared to healthy controls. Second, pancreatic fat is higher in people with type 2 diabetes compared with age-matched controls (5) and is negatively associated with insulin secretion (6). Third, accumulation of fat in the liver has been linked to resistance to insulin-mediated gluconeogenesis and development of type 2 diabetes (7).

These observations might be confounded by some unknown factors and therefore may not concur with the causal nature of the associations. These limitations can be avoided by using Mendelian randomization (MR) analysis given the assumptions are met. MR is a method that uses genetic variants reliably associated with exposures of interest to estimate a non-confounded causal association between the exposure (e.g. pancreatic fat) and an outcome (e.g. type 2 diabetes) (8). Since allelic variants remain stable over time, their lifetime effects on the exposure levels precede the outcome and limit bias from reverse causation.

Understanding the exact role of liver and pancreas in diabetes risk may be helpful to develop more effective prevention, prediction, and treatment, or to supplement existing pathophysiological knowledge on important conditions. MRI is an indispensable and non-invasive tool enabling for the measurement of liver and pancreas and advances in its automated analysis has made its measurement at scale a reality (10). The availability of MRI scans of liver fat in 32,859 UK Biobank participants has allowed us to understand the genetic contribution to variation in fat content and volume of liver and pancreas (10).

In this study, we aimed to measure the volume and fat content of the liver and pancreas in a large cohort of individuals with type 1 and 2 diabetes and use the largest available samples with genetic association results to test the causal role of liver and pancreas fat content and volume in the etiology of type 1 and type 2 diabetes using MR approach.

Research Design and Methods

Data Sources and Study Participants

The UK Biobank Study. We used data from the UK Biobank for the MRI study of liver and pancreas volume and fat content (13). For the current study, we included 32,859 individuals of white British ancestry who underwent the MRI imaging scan. Type 1 and type 2 diabetes were defined as binary outcomes from ICD-9 and ICD-10 medical billing codes. The UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) (http://www.ukbiobank.ac.uk/ethics/), and these ethical regulations cover the work in this study.

Image processing. The methods have been described in detail elsewhere (10). In preprocessing, we blended the six separate Dixon neck-to-knee acquisitions, applying bias field correction and automated correction of fat/water swaps. We used the PRESCO algorithm to estimate proton density fat fraction (PDFF) in the liver and pancreas multiecho slices. To segment organs, we manually annotated organs on the 3D Dixon neck-to-knee acquisition (liver) and T1-weighted 3D pancreas acquisition (pancreas). Annotations were manually inspected to ensure accuracy before use in modelling. We trained a modified U-net convolutional neural network on each modality, and applied this to data from all participants. We estimated volumes by counting voxels and multiplying by the size of each model.

GWAS of type 1 and type 2 diabetes. Summary-level association results were extracted from the largest publicly available GWAS of type 1 diabetes from the meta-analysis of 9,358 case and 15,705 controls (11) and type 2 diabetes from a recent meta-analysis of 55,005 cases and 400,308 controls of European ancestry (12). The UK Biobank participants were not part of these GWAS. Details on the demographics of the cohorts participating can be found in the respective publications.

FinnGen study. We used GWAS summary statistics from FinnGen (14) to validate our findings. The GWAS of type 1 diabetes included 2,649 cases and 183,674 controls, and the GWAS of type 2 diabetes included 29,166 cases and 183,185 controls. The definitions of disease and population characteristics are summarised in **supplementary table 1**.

Genetic instrument

We used genetic variants associated with four different exposures, including liver and pancreas fat content and volume. The GWAS has been described elsewhere (10) but in summary, we included participants who self-reported their ancestry as ‘White British’ and who clustered with this group in a principal components analysis. We used BOLT-LMM and included age at imaging visit, age squared, sex, imaging centre, scan date, scan time, and genotyping batch as fixed-effect covariates, and genetic relatedness as a random effect to control for population structure and relatedness.

For each instrument, we used independent variants associated ($p<5x10^{-8}$) with each exposure in the UK Biobank. This included 10 variants associated with liver fat (explained 4.6% of the observed variance), 11 variants associated with liver volume (2%), 9 variants associated with pancreas fat (1.9%), and 17 variants associated with pancreas volume (2.3%) (**supplementary table 2a**) (15). The minor allele frequencies of these variants ranged between 0.013 and 0.495.

We extracted estimates of these variants on risk of type 1 (11) and type 2 diabetes (12) (**supplementary table 2**). For genetic variants not present in these GWAS, we selected proxy SNPs in linkage disequilibrium (LD, $r^2 > 0.7$) using all European populations from 1000

Genomes phase 3, HapMap or a reference panel consisting of 379,396 individuals of European ancestry from the UK Biobank (**supplementary table 2b**).

Statistical analysis

To understand how liver and pancreas fat and volume are associated with risk of type 1 and type 2 diabetes, we performed a logistic regression adjusting for age, sex, height, and BMI, imaging centre, imaging date, and scan time.

To examine if the associations are likely causal, we used inverse-variance weighted (IVW) two-sample MR as our main analysis (16) to estimate the effect of a 1-standard deviation (SD) increase in the four exposures on risk of type 1 and type 2 diabetes. In the absence of horizontal pleiotropy (when the genetic variants are associated with the outcome through pathways other than the exposure) or when horizontal pleiotropy is balanced, the IVW method provides an unbiased effect estimate. In addition, we performed several sensitivity analyses, including weighted median, MR-Egger, mode-based estimate and MR-pleiotropy residual sum and outlier (MR-PRESSO), to assess and account for potential horizontal pleiotropy. All the analyses were performed using the *MendelianRandomization* package in R (20). We used the “random” model in IVW and MR-Egger (to allow for the presence of heterogeneity in our instruments) and used the “penalized” parameter to penalize variants with heterogeneous causal estimates. We performed MR-PRESSO using the *MR-PRESSO* package in R (21). In all the above analyses, effects were aligned to the exposure-increasing allele reported in previously published work (10).

Data and Resource Availability

Type 1 diabetes (https://www.ebi.ac.uk/gwas/publications/32005708), type 2 diabetes (https://diagram-consortium.org), pancreas and liver fat content/volume (accession numbers GCST90016666-GCST90016676, URL: http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90016666).

Results

Characteristics of 32,859 individuals of white British ancestry with MRI scan data from the UK Biobank are presented in **Table 1**. The mean age was 63.9 (SD 7.5) years, and 51.5% of participants were women. After adjusting for sex, imaging centre and scan date and time, liver and pancreas volume were negatively associated with age (-9.9 mL or -0.03 SD/year for liver volume and -0.54 mL or -0.03 SD/year for pancreas volume), pancreas fat was positively associated with age (0.22% or 0.026 SD/year), liver fat was positively associated with age until age 60 and from age 60 onwards there was a subtle decline in liver fat (**Figure 1**).

Liver fat

In our observational study using data from the UK Biobank, higher liver fat was associated with higher risk of type 2 diabetes (odds ratio (OR) per 1 SD (5.06%) higher liver fat: 2.16 [95% CI 2.02,2.31]); p=1e-105). The two-sample IVW MR provided evidence for a causal role of liver fat in risk of type 2 diabetes with an OR of 1.27 [1.08,1.49]; that is an average 27% increased risk of type 2 diabetes per SD higher liver fat (**table 2, figure 2a**). Sensitivity analyses using the weighted median (1.29 OR), MR-Egger (1.45 OR) and mode-based method (1.28 OR) provided similar results. There was no evidence of heterogeneity from MR-Egger. Using MR-PRESSO, we found evidence for pleiotropy ($p_{global\ test}$ <0.001). Results from MR-PRESSO after outlier correction were slightly stronger (three outliers removed (those near *APOE, GPAM*, and *C2orf16*), OR 1.27 [1.21,1.34], **supplementary tables 3 and 4**). The liver fat-increasing alleles at *GPAM* and *C2orf16* were associated with lower risk of type 2 diabetes (p=0.0043 and 8.3E-5, respectively, **supplementary figure 1**).

Observationally, higher liver fat was associated with lower risk of type 1 diabetes in the UK Biobank (OR 0.79 [0.65,0.96]; p=0.018). We did not find any evidence of causality between liver fat and risk of type 1 diabetes (OR 1.07 [0.90,1.27] per SD higher liver fat) (**table 2, figure 2b**). Results from the three sensitivity methods were similar. There was no evidence of heterogeneity from MR-Egger Using MR-PRESSO, we found no evidence for pleiotropy ($p_{global\ test}$=0.34) (**supplementary tables 3, supplementary figure 2**).

Liver volume

Observationally, higher liver volume was associated with higher risk of type 2 diabetes (OR 2.11 [1.96, 2.27] per 1 SD (1.38 L) higher liver volume; p=7e-90) in the UK Biobank. We did not find any evidence of causality between liver volume and risk of type 2 diabetes (OR 1.37 [0.82,2.27] per SD higher liver volume) (**table 2, figure 2a**). However, sensitivity analyses using the weighted median (1.42 [1.17,1.73]) and mode-based method (1.40 [1.11,1.77]) provided evidence for a causal association. There was no evidence of heterogeneity from MR-Egger Using MR-PRESSO, we found evidence for pleiotropy ($p_{global\ test}$<0.001). The outlier correction did not alter the inference of the results after removing six outliers (OR 1.44 [1.24,1.69]) (**supplementary tables 3 and 4, supplementary figure 3**). These variants included those near GSTA2, GCKR, and PDIA3 (where the liver volume-increasing allele was associated with lower risk of type 2 diabetes), and *MAU2, RSPO3* and 16:53812783 (where the liver volume-increasing allele was associated with higher risk of type 2 diabetes.

Observationally, there was no association between liver volume and type 1 diabetes (OR 1.04 [1.00,1.09]; p=0.065) and we did not find any evidence of causality (OR 0.92 [0.67,1.27] per SD higher liver volume) (**table 2, figure 2b**). Comparison of results from the three sensitivity methods indicated no evidence of pleiotropy. There was no evidence of heterogeneity from MR-Egger. Using MR-PRESSO, we found no evidence for pleiotropy ($p_{global\ test}$=0.15) (**supplementary tables 3, supplementary figure 4)**.

Pancreas fat

Observationally, higher pancreatic fat was associated with higher risk of type 2 diabetes (OR 1.42 [1.34,1.51] per SD (10.41%) higher pancreas fat; p=3e-31). However, we did not find any evidence of causality between pancreas fat and risk of type 2 diabetes (OR 1.02 [0.76,1.37]) (**table 2, figure 2a**). Similar results were obtained using the other three sensitivity methods. There was no evidence for unbalanced horizontal pleiotropy from the MR-Egger. Using MR-PRESSO, we found evidence for pleiotropy ($p_{global\ test}$<0.001). Removing of five outliers did not alter the inference of the results (OR 1.06 [0.87,1.29]) (**supplementary tables 3 and 4**). Among nine variants associated with pancreas fat, fat-increasing alleles at three variants (near *ABO, FAM25C*, and rs4733612) were associated with higher risk of type 2 diabetes (p=3.9E-7, 0.036, 2.6E-5, respectively), while pancreas fat-increasing alleles near *CEBPB, PEPD* and *PLEKHM3* were associated with lower risk of type 2 diabetes (p= 5.30E-06, 0.016, 0.0019, respectively) (**supplementary figure 5**).

Observationally, there was no association with risk of type 1 diabetes (OR 1.08 [0.87,1.35] per SD higher pancreas fat; p=0.49) and we did not find any genetic evidence of causality (OR 1.26 [0.82,1.93]) (**table 2, figure 2b**). Similar results were obtained using the sensitivity methods. The intercept from the MR-Egger regression test provided evidence for some unbalanced horizontal pleiotropy The Q test did not show evidence of heterogeneity in the effect of pancreas fat variants on type 1 diabetes (Q-statistic 7.8). Using MR-PRESSO, we found evidence for pleiotropy ($p_{global\ test}$=0.005) (**supplementary tables 3 and 4**). Removing one outlier did not alter the inference of the results (OR 1.47 [1.00,2.12]).

Pancreas volume

Observationally, higher pancreatic volume was associated with lower risk of type 2 diabetes (OR 0.73 [0.68, 0.78] per SD (0.06 L)) higher pancreas fat; p=1.31e-23). Consistently the two-sample IVW MR provided evidence for a causal role of pancreas volume in risk of type 2 diabetes with an OR of 0.76 [0.62,0.94] that is an average 24% decreased risk of type 2 diabetes per SD higher pancreas volume (**table 2, figure 2a**). Sensitivity analyses using the weighted median (0.81) and mode-based method (0.83) provided similar results. MR Egger yielded an OR of 0.22 [95% CI 0.11,0.43]. There was some evidence of heterogeneity from MR-Egger Using MR-PRESSO, we found evidence for pleiotropy ($p_{global\ test}$<0.001). Results from MR-PRESSO after outlier correction were slightly attenuated (three outliers removed, OR 0.83 [0.74,0.94]) (**supplementary tables 3 and 4**). The variants excluded were those near *RTL1, CTRB2* and *ABO*.

Observationally, higher pancreas volume was associated more strongly with lower risk of type 1 diabetes (OR 0.42 [0.36,0.48] per SD higher pancreas volume; p=3e-33) comparing to type 2 diabetes. However, we did not find any evidence of causality between pancreas volume and risk of type 1 diabetes (OR 1.55 [0.85,2.84]) (**table 2, figure 2b**). Similar results were obtained using the sensitivity methods. The MR-Egger regression did not provide strong evidence for unbalanced horizontal pleiotropy. Using MR-PRESSO, we found evidence for pleiotropy ($p_{global\ test}$<0.001). The MR estimates for type 1 diabetes did not alter the inference of the results after removing four outliers (OR 0.96 [0.67,1.36]) (**supplementary tables 3 and 4**).

All the MR results were replicated using FinnGen data (**supplementary table 5**).

Discussion

We provided genetic evidence that higher fat in the liver and lower pancreas volume were both causally associated with higher risk of type 2 diabetes. We did not identify evidence for a causal role of pancreas fat in type 2 diabetes risk or pancreas volume in type 1 diabetes risk. We used the largest study samples available and performed detailed investigation of possible violations of MR assumptions. We found evidence of pleiotropy for some variants and performed robust sensitivity analyses to test the assumptions of MR and corrected for it if violated.

Liver fat. The strong genetic evidence we found for a causal role of higher liver fat in risk of type 2 diabetes is consistent with recent MR studies showing a causal association between non-alcoholic fatty liver disease or its markers (alanine aminotransferase and aspartate aminotransferase) and higher risk of type 2 diabetes (22; 23). Using a unique genetic approach, we have recently identified 36 genetic variants associated with a favourable adiposity (higher adiposity but a favourable metabolic phenotype and lower risk of type 2 diabetes) and showed that lower liver fat is the key mechanism that protects against risk of type 2 diabetes and other related cardiometabolic diseases in spite of higher adiposity (24). Future work will be needed to expand MR from two-way analyses to a full causal network for type 2 diabetes, as the factors and co-morbidities influencing this disease, including risk for liver disease progression, are extraordinarily complex. The link between liver fat and type 1 diabetes as reported in previous studies is less clear with some limited and inconsistent data (25). In our observational analysis, we found a negative association between liver fat and risk of type 1 diabetes in UK Biobank. The explanation could be that de novo lipogenesis in the liver falls when insulin production stops in type 1 diabetes; therefore, liver fat change is a consequence of insulin loss rather than a cause in type 1 diabetes. Consistently, our results provide no evidence for a causal role of higher liver fat in risk of type 1 diabetes.

Liver volume. Although we did not find any evidence of a causal effect between liver volume and risk of type 2 diabetes in our main MR analysis, our sensitivity MR analyses that corrected for bias in our genetic instrument provided evidence for a causal association between higher liver volume and higher risk of type 2 diabetes. The link between higher liver volume and type 2 diabetes could however be a reflection of the correlation between higher liver fat and higher liver volume (r=0.20 [95% CI: 0.19,0.21] in our UK Biobank data) as well as the correlation between obesity and liver volume (26).

Pancreas fat. Observational studies of pancreatic fat provide inconsistent evidence regarding whether pancreatic fat is itself a driver of β-cell dysfunction and type 2 diabetes. Results from the Diabetes Remission Clinical Trial (DiRECT) in the UK demonstrated that the remission of type 2 diabetes was associated with a major reduction in liver triglyceride export and a small, but significant, decrease in pancreatic fat content (27). Conversely, weight regain and return of diabetes were shown to be associated with increased liver and pancreatic fat, and re-emergence of beta cell dysfunction (28). The sequence of events suggest that the disease process may be triggered by deposition of ectopic fat in the pancreas, causing β-cell dysfunction and type 2 diabetes (29). However, other studies indicate no association between type 2 diabetes and pancreatic fat using either CT or histology at autopsy (30). All these studies are based on small numbers of selected individuals and our study is the first large-scale one to examine the causal effect of pancreatic fat in diabetes risk. Our results may be consistent with the explanation that higher fat in the pancreas observed in people with type 2 diabetes is secondary to disease or a result of a higher general obesity, but there are some caveats as discussed below.

At the individual level, variants associated with higher pancreatic fat can be divided into two groups with opposite effect on risk of type 2 diabetes. Studies of these individual variants can provide further insight about the role of pancreatic fat in type 2 diabetes. The allele with

the strongest effect on pancreatic fat (in *PEPD*) was associated with lower risk of type 2 diabetes. This allele is also associated with higher body and trunk fat percentage (data from white British in the UK Biobank). The second pancreatic fat-increasing allele (near *CEBPB*) has been shown to be associated with lower risk of type 2 diabetes in a multi-ancestry analysis (31), but has not been shown to be associated with any other trait/disease. The third pancreatic fat-increasing allele is located in *PLEKHM3* and is not associated with any other trait/disease. However, it is not known whether these variants lead to differential location of fat within the pancreas. Previous studies have shown that fat distribution varies significantly between the head of the pancreas and its other sections (32). This heterogeneity may differentially impact pancreatic function and possibly the development of type 2 diabetes.

Pancreas volume. Our results provide the first genetic evidence that the decrease in pancreas volume may be causal to type 2 diabetes. Our results support the hypothesis that underlying mechanisms associated with reduced pancreatic volume precede diagnosis of type 2 diabetes. However, we did not see any evidence for a causal role of reduced pancreas volume in the risk of type 1 diabetes, which could be explained by two main factors. First, our genetic instrument for pancreas volume is based on MRI scan data of pancreas in adults with a mean age of 63.8 ± 7.52 years. It is possible that adult pancreas volume does not correlate with pancreas volume in childhood when type 1 diabetes starts. However, observationally, pancreas volume had a stronger association with the risk of type 1 diabetes versus type 2 diabetes in our data. Second, we had less power to detect a causal association with risk of type 1 diabetes compared to type 2 diabetes (9,358 cases vs 55,005 cases, respectively). However, the direction of effect from the MR study was not consistent with a tentative causal effect between reduced pancreas volume and higher risk of type 1 diabetes. The variant with the strongest effect on pancreas volume is located near *CTRB2* and has opposing effects on risk of type 1 and 2 diabetes; the pancreas volume-increasing allele is associated with lower risk of type 2 diabetes and higher risk of type 1 diabetes. Given that the pathogenesis of type 1 and 2 diabetes are clearly different, this could signify that the process driving the development of the former, probably autoimmune reaction, may override any effect of organ size. Furthermore, there may be some variants linked to higher volume that may also be linked to greater likelihood of an autoimmune reaction. The minor allele of a correlated variant (rs7202877; r^2=0.66) has been identified previously to be a risk factor for type 1 (34) and a protective factor for type 2 diabetes (35). The protective effect of the allele against type 2 diabetes has been reported to be associated with GLP-1-stimulated insulin secretion (36). Moreover, a recent interventional study has shown that weight gain and prolonged diabetes duration often lead to smaller pancreases, while weight loss reverses this effect, a supportive narrative of the relationship of pancreatic size and type 2 diabetes (37), although our work adds support for pancreatic size being causal for type 2 diabetes so opening the potential for a bidirectional relationship.

Our study had some limitations. (i) We used organ volume and fat content measured in adulthood which could bias the association with type 1 diabetes towards the null effect. (ii) For some genetic variants we used as instruments, the causal genes and therefore the biological mechanisms are unknown which makes it difficult to test bias and pleiotropy. However, we used rigorous sensitivity tests that supported the main results. (iii) Our measurement of pancreas volume does not differentiate between endocrine and exocrine pancreas and more specific data are needed to understand the role of β-cell mass or exocrine inflammation in mechanisms that link reduced pancreas volume to higher risk of diabetes. (iv) The phenotyping of liver and pancreas volume/fat was performed on tractable measures derived from image segmentation. Although it is possible that some imaging artefacts are introduced in the results, any variance due to this is likely negligible given the size of the cohort and could not have affected our genetic instruments. (v) Using 3 point Dixon MRI of the pancreas, we may not have perfectly captured the pathological areas of pancreatic fat comparing to more sophisticated technique of MR image ‘biopsy’ method

(MR-opsy) (32). However, MR-opsy is not practical for the very large cohorts required for genetic studies, the scale of which demands automated analysis and the overall impact of the method we used in the current study on the PDFF values and therefore the genetic associations would be minimal. (vi) The small difference (around 1.25-fold) of pancreas fat content between people with and without type 2 diabetes, and the wide range between individuals raises the question of sensitivity of our approach to detect a genuine difference. By taking a Mendelian randomization approach and using a strong instrument for pancreas fat and a large sample size, we had 99% power to detect any association between pancreas fat and risk of type 2 diabetes. However, we suggest replication of the association between the instrument and pancreas fat in an independent cohort would be valuable. (vii) The MRI-derived phenotypes represent the tissue as a whole, and do not investigate within-organ heterogeneity, e.g. differences in the regional distribution of fatty deposits within the liver and pancreas, or differences in cell type or tissue sections. Also, the present set of parameters do not account for differences in organ shape or position. (viii) This study was conducted in a cohort of European ancestry. Even modest differences across populations in contributions of common variation to complex traits necessitates broadening the diversity of populations studied (38). Therefore, our findings are only generalizable to European population. Finally, change in liver and pancreas fat content or volume could also be affected by pathophysiological mechanisms secondary to type 1 or type 2 diabetes. For example, subclinical exocrine inflammation of the pancreas associated with insulitis (39), as well as insulin deficiency and the lack of a trophic effect on pancreas exocrine tissue (3), could contribute to reduced pancreatic volume in type 1 diabetes, while atherosclerosis might cause reduction in pancreas in type 2 diabetes (40). Future MR studies investigating the role of type 1 and 2 diabetes on changes in these features are needed to understand the role of other mechanisms or if there is a mutual causal effect. We hope other groups can validate or expand our findings in relevant datasets, should they exist with sufficient power.

In summary, our results are in line with a causal role for higher liver fat and reduced pancreas volume in type 2 diabetes etiology and show consistency in sensitivity analyses. Given the worldwide increasing prevalence of type 1 and type 2 diabetes, better understanding of the underlying mechanisms involving liver and pancreas volume and fat content may provide new insights in preventing and treating diabetes.

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Tables

Table 1. Study population characteristics, UK Biobank. SD: standard deviation.

	Liver fat	**Liver volume**	**Pancreas fat**	**Pancreas volume**
Number of participants	32,858	32,860	25,617	31,758
% Female	51.5	51.5	51.2	51.4
Age (years), mean (SD)	63.9 (7.52)	63.9 (7.52)	64.2 (7.48)	63.8 (7.52)
BMI (Kg/m^2), mean (SD)	26.5 (4.36)	26.5 (4.37)	26.5 (4.31)	26.5 (4.34)
Height (cm), mean (SD)	169 (9.26)	169 (9.26)	169 (9.26)	169 (9.25)
Type 2 diabetes, n (%)	1002 (3.53)	1004 (3.52)	716 (3.33)	968 (3.54)
Type 1 diabetes, n (%)	117 (0.41)	118 (0.41)	73 (0.34)	114 (0.42)
Mean (SD) of the image derived phenotype in all	5.06% (5)	1.38(L) (0.3)	10.41% (7.9)	0.06(L) (0.018)
Mean (SD) of the image derived phenotype in females	4.43% (4.7)	1.28(L) (0.25)	8.34% (6.7)	0.06(L) (0.016)
Mean (SD) of the image derived phenotype in males	5.73% (5.2)	1.49(L) (0.3)	12.6% (8.5)	0.06(L) (0.019)

Table 2. Results of the MR study testing causal association between liver and pancreas fat/volume and type 1 and type 2 diabetes.

Analysis	OR	Lower CI	Upper CI	P	Egger intercept	Heterogeneity: Q	I^2 Egger
Liver fat vs. type 2 diabetes							
IVW	1.269	1.079	1.492	0.018		80.4, p<0.001	
Weighted median	1.288	1.207	1.375	3E-14			
MR Egger	1.450	1.142	1.842	0.016	-0.020, p=0.19	64.1, p<0.001	0.98
MBE	1.283	1.204	1.369	3E-14			
Liver fat vs. type 1 diabetes							
IVW	1.066	0.896	1.268	0.49		11.5, p=0.24	
Weighted median	1.087	0.891	1.325	0.41			
MR Egger	1.025	0.772	1.360	0.87	0.006, p=0.73	11.4, p=0.18	0.98
MBE	1.057	0.882	1.267	0.55			
Liver volume vs. type 2 diabetes							
IVW	1.366	0.822	2.270	0.26		305.6, p<0.001	
Weighted median	1.418	1.165	1.725	0.00048			
MR Egger	0.959	0.320	2.873	0.94	0.028, p=0.49	289.0, p<0.001	0.70
MBE	1.400	1.106	1.773	0.0052			
Liver volume vs. type 1 diabetes							
IVW	0.922	0.669	1.270	0.63		15.8, p=0.11	
Weighted median	0.819	0.583	1.150	0.25			
MR Egger	0.884	0.435	1.797	0.74	0.003, p=0.90	15.8, p=0.07	0.68
MBE	0.826	0.545	1.252	0.37			
Pancreas fat vs. type 2 diabetes							
IVW	1.019	0.757	1.373	0.90		86.2, p<0.001	
Weighted median	0.956	0.810	1.129	0.60			
MR Egger	2.227	0.387	12.827	0.40	-0.052, p=0.40	77.5, p<0.001	0.35

MBE	0.870	0.681	1.110	0.26			
Pancreas fat vs. type 1 diabetes							
IVW	1.255	0.818	1.925	0.33		22.2, p=0.005	
Weighted median	1.656	1.120	2.449	0.011			
MR Egger	0.072	0.015	0.351	0.014	0.191, p=0.01	7.8, p=0.35	0.28
MBE	1.895	0.796	4.514	0.15			
Pancreas volume vs. type 2 diabetes							
IVW	0.761	0.620	0.935	0.02		83.1, p<0.001	
Weighted median	0.805	0.693	0.934	0.004			
MR Egger	0.220	0.112	0.433	0.00063	0.069, p=0.002	42.2, p=0.0001	0.00
MBE	0.825	0.639	1.066	0.14			
Pancreas volume vs. type 1 diabetes							
IVW	1.550	0.845	2.844	0.18		86.8, p<0.001	
Weighted median	1.159	0.735	1.826	0.53			
MR Egger	13.425	1.159	155.453	0.057	-0.121, p=0.10	70.8, p<0.001	0.35
MBE	0.871	0.429	1.771	0.70			

The odds ratio (OR) are per 1 standard deviation higher liver and pancreas fat/volume. CI: 95% confidence interval; IVW: inverse-variance weighted; MBE: mode-based estimate; MR: Mendelian randomisation.

Figures

Figure 1. A: Relationship between liver and pancreas fat and volume and age within the UK Biobank. Each trait is standardised, so that the y axis represents standard deviations, after adjustment for imaging centre and date. The trend is smoothed using a generalised additive model with smoothing splines for visualisation purposes. B: The density plots of liver and pancreas fat and volume in type 1 and type 2 diabetes cases and controls within the UK Biobank study.

Figure 2. The inverse-variance weighted, weighted median, Egger and mode-based two-sample Mendelian randomisation (MR) results for (A) type 2 diabetes and (B) type 1 diabetes. Only 16 of the 17 pancreas volume SNPs were present in each GWAS. The error bars represent the 95% confidence intervals (CI) of the MR estimates in odds ratio (OR) per standard deviation change in genetically determined liver and pancreas fat/volume. SNP, single nucleotide polymorphism.

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