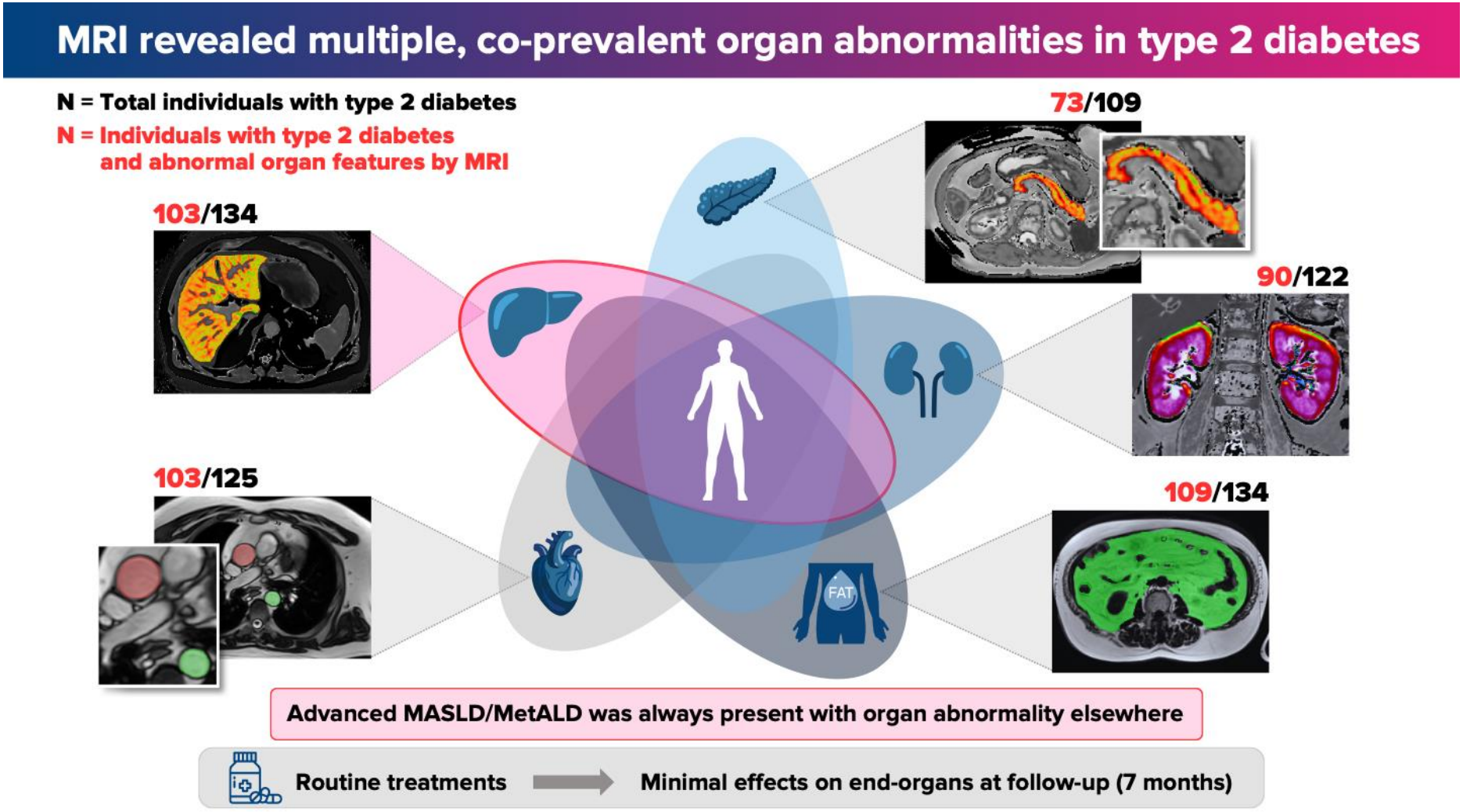
Graphical abstract illustration: MRI revealed multiple, co-prevalent organ abnormalities in type 2 diabetes.



Title: Quantitative imaging reveals steatosis and fibro-inflammation in multiple organs in people with type 2 diabetes: a real-world study.

Short title: Multi-organ abnormalities in type 2 diabetes

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Abstract

We aimed to determine the extent of multi-organ fat accumulation and fibro-inflammation in individuals living with type 2 diabetes. We deeply phenotyped individuals with type 2 diabetes (134 from secondary care, 69 from primary care) with multi-organ, quantitative multi-parametric MRI and compared with 134 matched controls and 92 normal weight controls. We examined the impact of diabetes duration, obesity status and glycemic control. Ninety-three of the individuals with type 2 diabetes were re-evaluated at 7 months (median). Multi-organ abnormalities were more common in individuals with type 2 diabetes (94%) than in age, BMI-matched healthy or healthy normal weight people. We demonstrated a high burden of combined steatosis and fibro-inflammation, within the liver, pancreas and kidneys (41, 17 and 10%), associated with visceral adiposity (73%) and poor vascular health (82%). Obesity was most closely associated with advanced liver disease, renal and visceral steatosis, and multi-organ abnormalities whilst poor glycaemic control was associated with pancreatic fibro-inflammation. Pharmacological therapies with proven cardiorenal protection improved liver and vascular health unlike conventional glucose-lowering treatments, whilst weight loss or improved glycaemic control reduced multi-organ adiposity ($p \leq 0.01$). Quantitative imaging in people with type 2 diabetes highlights widespread organ abnormalities and may provide useful risk and treatment stratification.

Trial Registration: ClinicalTrials.gov Identifier: NCT04114682

Keywords: Type 2 diabetes, non-alcoholic steatohepatitis (NASH), metabolic-dysfunction associated steatohepatitis (MASH)/steatotic liver disease (MASLD), pancreas, kidney, CKD, CVD, cT1, magnetic resonance imaging, SGLT2 inhibitors, GLP-1 receptor agonists.

Article highlights

- Why did we undertake this study? Type 2 diabetes is a multisystem disease, but multi-organ imaging studies are lacking.
- What is the specific question we wanted to answer: To quantify organ abnormalities (steatosis and fibro-inflammation) in type 2 diabetes using multi-parametric magnetic resonance imaging (mpMRI).
- What did we find? In 126 of 134 individuals with type 2 diabetes multi-organ abnormalities (steatosis and fibro-inflammation) were detected with mpMRI. This persisted despite glucose-lowering therapy over 7 months.
- What are the implications of our findings? The therapeutic impact of new diabetes therapies on preventing or reversing end-organ damage can be measured by mpMRI.

Type 2 diabetes, as a multi-system cardiometabolic disease, causes a significant burden of microvascular and macrovascular disease with substantial end-organ damage. Surveillance of cardiovascular and renal complications is a clinical priority. In >4.5 million individuals with type 2 diabetes, cardiovascular disease (CVD) prevalence was estimated at 32%, accounting for ~50% of the total deaths (1). Similarly, incident chronic kidney disease (CKD) occurred in 36% of >1.1 million European individuals with type 2 diabetes (2).

The role of liver fat accumulation in the pathophysiology of type 2 diabetes has been widely recognised (3), and more recent clinical focus has shifted to considering metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD prevalence is 56% globally (4), with a low but inherent risk of severe liver disease (increased incidence of fibrosis (5), of hepatic decompensation or hepatocellular carcinoma (6)) in individuals with type 2 diabetes. This need to assess liver health is reflected in guidelines (7,8). Similarly, individuals with type 2 diabetes are also at higher risk of pancreatic disease (acute pancreatitis and pancreatic ductal adenocarcinoma (PDAC)) but these outcomes are rarer (9).

Current focus of treatment of individuals with type 2 diabetes has shifted away from the traditional glucocentric approach (targeting reductions in HbA1c, a downstream intervention) to a weight centric and holistic approach (an upstream intervention). This approach recognises obesity as a key pathophysiological driver of type 2 diabetes and its associated metabolic complications. The newer drug classes for type 2 diabetes, the sodium-glucose co-transporter 2 inhibitors (SGLT2i) (10) and glucagon-like peptide 1 receptor agonists (GLP-1 RA) (11), aside from their glucose-lowering effects are associated with significant weight loss, and both these mechanisms contribute to benefits on the heart, kidneys and liver (12,13). However, little is known about overall health changes even with optimal management of diabetes.

Multi-parametric MRI (mpMRI) serves as a non-invasive, reproducible tool for the quantitative assessment of organ manifestations associated with obesity, prediabetes or diabetes, or indeed

any multi-system disease, providing quantitative analysis of tissue composition (14,15). Aside from assessment of body composition (differentiating between subcutaneous and visceral adipose tissue, SAT and VAT)(16), mpMRI has commonly been used for organ tissue characterisation. Proton density fat fraction (PDFF) is a quantitative measure of fat (16,17) used predominantly as a clinical trial endpoint in the liver and pancreas, including trials with the latest dual and triple agonists and weight loss drugs (23,24) while T1 mapping mpMRI methods have been developed in the liver, pancreas and kidney.

Increases in T1 relaxation time acquired without contrast, reflecting increased water content in biological tissues, can be indicative of oedema, inflammation and/or fibrosis (collectively termed fibro-inflammation)(20). Iron-corrected T1 (cT1) is a marker of fibroinflammatory change in MASLD guidelines and guidance (7,21,22); cT1 has sensitivity to fat but correlates with liver disease activity from pathology (23,24) and has been shown to predict liver-related outcomes in MASH (25) and CVD outcomes (26). In the pancreas, increased T1 relaxation time discriminates acute pancreatitis, resolving in response to anti-inflammatory treatment (27), can stage chronic pancreatitis (28) and pancreatic fibrosis (29), and correlates with reduced exocrine function in PDAC and chronic or autoimmune pancreatitis (30). In the kidney, increased T1 correlates with a reduction in renal function (by eGFR)(31), is diagnostic of CKD (32) and is elevated in the cortex relative to the medulla in kidneys with interstitial fibrosis (33).

The prognostic relevance of perirenal and renal sinus fat deposition and its relationship with an increased risk of CKD in individuals with type 2 diabetes has also been shown with mpMRI (32,34). MpMRI has also provided metrics of vascular health that have been extensively validated as independent predictors of incident cardiovascular events and are diagnostic of atherosclerosis and aortic aneurysms (35,36).

The aim of the current study was to determine the underlying burden of ectopic fat and fibro-inflammation affecting the liver, pancreas and kidneys and to assess the relationship with visceral adiposity, and vascular health, using mpMRI in individuals with type 2 diabetes in comparison with age- and BMI-matched and normal weight people without type 2 diabetes. Additionally, as a secondary aim we evaluated the impact of clinical features and of changes in weight, glycaemic control or drug therapy on underlying multi-organ health.

RESEARCH DESIGN AND METHODS

Study design and participants

MODIFY (clinical trial registration number: NCT04114682) was a real-world, multi-centre study adopting a prospective, longitudinal, observational cohort study design in individuals with type 2 diabetes. There was no intervention to the standard of care. Adult individuals with type 2 diabetes on glucose lowering therapy were recruited from secondary care settings (119/134 individuals) and the community (15/134 individuals), between January 2020 to March 2022. Exclusion criteria were hepatitis, Wilson's disease, haemoglobinopathies, known renal tract abnormalities, excessive alcohol intake, and contraindication to MRI scanning. The three participating centres were University Hospital Aintree, Liverpool, Oxford University Hospitals (OUH) NHS Foundation Trust and Royal Free NHS Foundation Trust.

All individuals with type 2 diabetes attended a baseline clinical assessment (blood and urine samples, medical history and anthropometrics, MRI; Supplementary Figure S1). All were invited for follow-up with clinical and MRI data collected at a single visit after baseline, funding permitting.

Comparison groups For comparison, we studied three additional groups: 69 matched controls with type 2 diabetes (ICD-10 codes E11.0 – E11.9) from the general population (UK Biobank, matched for age, sex, ethnicity and BMI) (43), 134 matched controls without type 2 diabetes

and 92 healthy volunteers (COVERSCAN, clinical trial registration number: NCT04369807; (15)). These participants had MRI scanning and clinical data collection, but no prospective plasma or urine biochemistry was performed, although HbA1c values were imputed from earlier visits, as previously (26). MRI data for liver and pancreas were available from the UKBB, but not for body adiposity composition, the aorta nor the kidneys.

Data collection

Biochemistry analysis HbA1c, renal profile, liver function tests, lipids and N-terminal pro B-type natriuretic peptide (NT-proBNP) were measured through accredited clinical laboratories. Metabolic syndrome was defined as per guidelines (38). Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of <60ml/min/1.73 m^2 and/or a urine albumin creatinine ratio (ACr) ≥30 mg/g (39).

MRI acquisition and analysis At both visits, all individuals with type 2 diabetes and healthy volunteers had a standardised multiorgan multiparametric MR scan (15)(CoverScan, Perspectum, Oxford), which lasted approximately 35 minutes with methods previously demonstrated for the healthy volunteers and the UK Biobank (14,15). All quantitative multi-organ MRI methods were deployed on standard clinical MRI scanners (Siemens Prisma 3T, Siemens Skyra 3T, Siemens Area 1.5T or a GE Signa Voyager 1.5T), and data acquired and processed by trained MR technologists and radiographers. Data was centrally curated and quality controlled.

Reproducibility of MRI metrics Scan-rescan repeatability of the metrics was evaluated in the healthy volunteers using standardised performance testing criteria to derive repeatability coefficients (15). Incidental findings were reported and reviewed by an expert radiologist.

Definition of normal organ parameters Normal values/reference ranges for MRI metrics for each organ were defined relative to reference ranges from the 92 healthy volunteers (Supplementary Table S1).

Liver In individuals with a cardiometabolic risk factor, advanced MASLD and MetALD were imaging-based definitions with both liver fat ≥5% and liver disease activity (cT1) ≥800ms, previously shown to be diagnostic of steatohepatitis in biopsy-paired datasets (23), in the absence or presence, respectively, of high consistent alcohol intake as per multi-society recommendations (40). An additional threshold of liver disease activity ≥875ms was also applied, which is associated with risk of liver fibrosis in biopsy-paired datasets (23). Liver volumes were also assessed but not included in definition of liver MRI abnormality (15).

Pancreas Metrics of pancreas fat (PDFF) and fibro-inflammation (srT1) were collected and elevation in either defined pancreatic abnormality, with disease defined as both steatosis and fibro-inflammation. Scanner referencing to derive srT1 includes (a) a scanner normalization step, which involves referencing to a specific MRI scanner of the same field strength; and (b) a field strength adjustment step to 3T, when applicable.

Kidney Metrics of renal sinus fat volume and fibro-inflammation in the renal cortex (cortical T1) were collected for both kidneys, and elevation in either defined renal abnormality, with disease defined as both steatosis and fibro-inflammation.

Aorta Distensibility was determined at three positions: proximal ascending, proximal descending, and abdominal aorta (36,41), and reduction at any position was considered a stiff, unhealthy aorta. The diameter lumen at systole was measured at the abdominal position; >3cm defined aortic abdominal aneurysm, as per guidelines.

Body composition Cross-sectional areas of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were determined from a single 2D section positioned at the third lumbar (L3) vertebrae (this region has been shown to be strongly associated with whole-body skeletal muscle distribution and to accurately estimate total SAT and VAT volumes (16)). Elevation in either defined abnormal body composition.

Definition of clinically significant differences (or outcomes) From recent guidelines (42,43) in type 2 diabetes we considered a relative change of 10% body weight or a return to HbA1c levels of <7% (53mmol/mol) as a clinically meaningful outcome, although a relative reduction of 5% in weight and absolute reduction of 0.9% in HbA1C were also investigated as these were the usual indicators in our real-world hospital settings.

Statistical analysis

Statistical power The study was powered for the primary endpoint: to evaluate liver disease activity (measured by cT1) in individuals with type 2 diabetes compared to matched controls without type 2 diabetes. A priori, we performed a power calculation for a group difference in liver cT1 between the baseline type 2 diabetes cohort and healthy controls matched for sex, BMI and age at 90% power and alpha of 0.05. At the final sample size of n=134 per group, this enabled a minimum detectable group difference of 33ms.

Statistical methods The descriptive statistics for continuous and categorical variables are expressed with the mean (SD) and frequency (percentage prevalence), respectively. For groupwise comparisons, Wilcoxon rank sum tests were applied for continuous variables and Fishers exact tests for categorical variables. For groupwise comparisons between the type 2 diabetes group and unmatched healthy volunteers linear and logistic regression models were used to statistically control for differences in age, sex, ethnicity, and BMI, to evaluate differences in continuous and categorical variables respectively. Statistical significance was defined by a p-value threshold of <0.05 (2-sided). All statistical analyses were conducted in R software version 4.2.1.

Data and resource availability

All data relevant to the study are included in the article or uploaded as online supplemental information.

RESULTS

Study population

Demographics

People with type 2 diabetes from real-world cohort One hundred and thirty-four individuals with type 2 diabetes mainly from secondary care underwent baseline evaluation (mean age 61 years, 41% female, 87% Caucasian, mean BMI of 32 kg/m^2, 5% smokers) (Table 1). Over half (55%) had a duration of type 2 diabetes of >10 years and 22% with a duration of <5 years (Supplementary Table S2).

Matched controls and healthy volunteers We compared metabolic co-morbidities and MRI organ metrics with 134 matched controls without type 2 diabetes (mean age 61 years, 46% female, 83% Caucasian, mean BMI of 32 kg/m^2, 6% smokers) and 69 matched controls with type 2 diabetes (mean age 62 years, 45% female, 94% Caucasian, mean BMI of 31 kg/m^2, 6% smokers, 51% with hypertension, 46% obese) from the general population. The latter presented with acceptable glycaemic control (mean 6.9% (0.9) HbA1c and 5-year (4) diabetes duration) (Supplementary Table S2). We also compared with 92 healthy volunteers of normal weight (mean age 44 years, 66% female, 92% Caucasian, mean BMI of 23 kg/m^2, 3% smokers).

Characteristics of real-world type 2 diabetes cohort

Blood pressure Almost half (63/133, 47%) of all individuals were on hypertension medications. Hypertension was prevalent: 52% of individuals exhibited a systolic blood pressure ≥140mmHg (Figure 1), of whom 35/69 were on hypertension medications. Diastolic blood pressure levels were lower (14% of individuals had ≥90mmHg). Hypertension prevalence was similar whether individuals with type 2 diabetes were from hospital or from the general population (Supplementary Tables S2).

Biochemistry The mean HbA1c was 8% (63 mmol/mol), with 83% of the cohort being greater than 6.5% (48 mmol/mol), with marginally worse glycaemic control evident with longer

duration disease (mean 7.5% if the duration was <10years vs 8.2% if ≥10 years, p<0.001). Glycaemic control was worse in the hospital setting compared to individuals from the general population (Supplementary Table S2). A pre-existing diagnosis of metabolic syndrome was common in this population (77%) and 12 individuals (9%) had mild to moderate (GFR stage 3 or higher) CKD, of which 3 with concomitant albuminuria.

Drug therapies Patient management comprised 30 different stable, combinations of glucose-modifying drugs (Figure 1). A third of the cohort were on metformin alone and metformin was used in combination with other drug classes in 56%. Almost half (49%) of the individuals with type 2 diabetes were on either SGLT2i or GLP-1 RA or both. Treatment allocation to SGLT2i and or GLP-1 RA was more frequent in those with longer duration type 2 diabetes (mean 14 *vs.* 8 years duration, p-value: <0.001) and worse glycaemic control (mean HbA1c 8.2% *vs.* 7.5% [66 *vs.* 58mmol/mol] p-value: 0.006), compared to allocation to metformin alone.

Individual organ MRI metrics

Liver Based on imaging, hepatic steatosis was present in 94 of 134 (70%) and liver disease activity at thresholds diagnostic of steatohepatitis (advanced MASLD/MetALD) (23) was present in 53 of 128 (41%). These proportions were higher compared to healthy volunteer controls (0/92, 0%) and matched controls without type 2 diabetes (17/134, 13%) (Table 1). Liver disease activity at thresholds diagnostic of steatohepatitis and significant fibrosis (23) was prevalent in 23% of individuals. Advanced MASLD/MetALD was more frequent in individuals with obesity, but not in those with longer diabetes duration or poor glycaemic control (Figure 2). The advanced MASLD/MetALD group had a higher BMI (33 kg/m^2 *vs.* 30kg/m^2) and liver biomarkers AST and ALT outside normal ranges but significant elevation in FIB-4 score was not observed (Supplementary Table S3, Figure 3). Advanced MASLD/MetALD prevalence was similar with and without hypertension (40% with vs 44% without, p=0.594). Separate analysis of individuals with type 2 diabetes from the general

population indicated that advanced MASLD/MetALD was slightly less prevalent (32% compared to 41% in our prospective hospital cohort, p=0.22) (Supplementary Table S2).

Pancreas Abnormal organ characteristics in the pancreas were also very common (73/109, 67%), with proportions significantly higher than in healthy volunteers (12/92, 13%) (Table 1). Pancreatic steatosis was frequent (70/112, 63%), and was independent of BMI status, glycaemic control or duration of diabetes (Figure 2). Fibro-inflammation (in 20/99, 20%) occurred where glycaemic control was poor (Figure 2) and was more frequent than in healthy volunteers (2/93, 2%) or matched non-diabetic controls (17/134, 13%). Pancreatic disease with both steatosis and fibro-inflammation was prevalent in 17% (17/102), of whom all (100%) had poor glycaemic control (HbA1c >6.5%). These findings were significantly more prevalent in our prospective hospital setting compared to type 2 diabetes in the general population (6% pancreatic disease, p=0.035; Supplementary Table S2). Hypertension did not discriminate pancreatic disease (18% vs 16%, p>0.99).

Kidney Abnormal tissue characteristics in the kidneys were present in 90 of 122 (74%) of individuals and more frequent than in healthy volunteers (5/81, 6%) (Table 1**)**. This was due to renal fibro-inflammation (26/133, 20%) or steatosis (77/121, 64%). Obesity was associated with steatosis in the kidneys (Figure 2). Thirteen of 132 (10%) individuals with type 2 diabetes had renal disease, with both steatosis and fibro-inflammation, compared to none of the healthy volunteers, but eGFR was low in only 2. Hypertension did not discriminate renal disease, renal steatosis nor fibro-inflammation (all p>0.5).

Aorta No individuals had abdominal aortic aneurysms. Stiffness of the aorta (low distensibility) was very frequent (103 of 125, 82%) in the individuals with type 2 diabetes, particularly in the proximal position and in those longer disease duration (Table 1, Figure 2), compared to healthy volunteers (5/75, 7%). Half (62/124) of individuals with a stiff aorta also had hypertension, and hypertension did not discriminate those with aortic stiffness (p=0.101).

SAT/VAT High visceral or subcutaneous adipose tissue were very frequent (109 of 134, 81%, respectively), particularly in those with obesity, or for SAT only with shorter disease duration (Table 1, Figure 2), compared to only 6% of healthy volunteers. Hypertension did not discriminate prevalence of high VAT or SAT ($p=0.053$, $p>0.5$, respectively).

Co-prevalence of abnormal organ features

Single/multiple organ involvement Overall, imaging showed that all 134 (100%) individuals with type 2 diabetes had abnormal tissue characteristics in at least one organ at baseline and 126 of 134 (94%) in at least two organs (Figure 3). One hundred and nine of 134 (81%) had abnormal tissue characteristics in at least three organs, particularly when they were also living with obesity (Figure 2). In contrast, routine biomarkers informing on the same organs without MRI indicated that only 58/134 (43%) had abnormal values in at least 3 organs, even if almost all (132/134, 99%) had abnormal value in at least 1 organ (Figure 3).

Involvement of other organs in advanced MASLD Having advanced MASLD was always associated with abnormal tissue characteristics in at least one other organ site (Figure 3**)**. Most common was advanced MASLD with elevated renal steatosis in the right kidney (69% with advanced MASLD vs. 48% without, p-value: 0.036) and higher VAT (281cm^2 with advanced MASLD *vs.* 225cm^2 without, p-value: 0.002) (Supplementary Table S3). Renal and pancreatic fibro-inflammation overlapped with advanced MASLD in 19% and 15% of individuals with advanced MASLD, respectively. Only 5 of 17 individuals with pancreatic disease also had advanced MASLD, and 6 of 13 individuals with renal disease had advanced MASLD.

Forty-six participants had at least one incidental finding (kidney and liver involvement were most common), of which at least 9 (6.7%) were recommended for further targeted clinical assessment, resulting in 1 partial nephrectomy for renal cancer with complete recovery. Eight of 9 cases (89%) had a stiff aorta and either a co-prevalent liver or kidney abnormality or both; one case (11%) had co-prevalent advanced MASLD.

Changes in multi-organ health over 7 months

Clinical characteristics A total of 93 individuals (69%) identified at baseline returned for follow-up evaluation (with similar clinical characteristics overall; Supplementary Table S4). The mean time from baseline to follow-up assessment was 218 days (SD: 44). In the follow-up group, treatment allocation did not substantially change, with 13 (14%) individuals on different treatments at follow-up. Anthropometrics and routine biomarkers showed negligible differences between baseline and follow-up. Few individuals with type 2 diabetes showed clinically meaningful outcomes in weight (3/93, 3% lost 10% body weight) or blood glucose (6/82, 7% returned to HbA1c ,7%) although more individuals displayed meaningful change (lost 5% weight or changed by 0.9% HbA1c; Figure 4).

MRI features of organ health Prevalence of abnormal organ features did not substantially change; for example, advanced MASLD prevalence in the follow-up group was 42% at baseline and 45% after 7 months (Supplementary Table S4). While overall changes were small in most cases, those with ≥5% weight loss has showed improvements in VAT and SAT ($p<0.001$) and liver steatosis ($p=0.011$) (Figure 4). Similarly, better glycaemic control (HbA1c ≥0.9%) improved mainly liver steatosis ($p<0.001$) but also renal steatosis ($p=0.01$) and VAT ($p=0.01$). Small, statistically significant improvements in aortic stiffness, visceral adipose tissue, liver disease activity and liver size were observed in individuals with type 2 diabetes on SGLT2 inhibitors and/or GLP1 RA medications, compared to all other treatments (mainly those on metformin alone, Figure 4). Of 14 individuals that had an abnormality in all organs at baseline, all abnormalities remained at follow-up in all except in 4 on SGLT2i/GLP1-RA in whom liver disease activity returned to normal levels (Figure 5).

DISCUSSION

In this quantitative, 'real-world', multi-organ MRI assessment study of liver, kidney and pancreas tissue composition, aortic distensibility and visceral/subcutaneous adiposity in

individuals living with diabetes and obesity, we demonstrate a significant cumulative burden of multimorbidity with multiorgan abnormalities. These were more pronounced than in age- and BMI-matched individuals and in healthy controls, highlighting the deleterious and widespread impact of poor underlying metabolic health. The multi-organ accumulation of fat and associated fibro-inflammation, occurring secondary to obesity and poor glycaemic control, highlights a likely mechanism for long-term organ damage, e.g., CKD, liver fibrosis/cirrhosis and CVD, and for the increased risk of hepatobiliary and renal malignancy.

Two recent studies have suggested that SGLT2i and GLP1- RA in individuals with type 2 diabetes and MASLD have protective effects: against adverse liver (44) and cardiovascular and mortality outcomes (45). In our study, multi-organ abnormalities were evident in almost every individual (94%), despite multiple, glucose-lowering treatments (Graphical abstract illustration), recognising a predictable cluster of multi-organ risk factors with a more global, 'whole-body' assessment. A non-invasive, comprehensive approach, using mpMRI to simultaneously examine the health of multiple organs, could avoid the need for multiple outpatient visits, organ-specific imaging (e.g., separate renal and liver ultrasonography) and the potential need for (liver/renal) biopsy with their inherent risks.

We previously showed both liver and pancreas fat are elevated in people with type 2 diabetes (16). Furthermore, liver disease activity, measured by cT1, is more widely representative of multi-organ health including in the heart and brain and can predict cardiovascular outcomes (14,26). In our study, liver involvement was frequently indicative of widespread abnormality. Advanced MASLD/MetALD was present in 41% of individuals and universally accompanied by abnormal organ tissue characteristics elsewhere (e.g., kidneys and/or pancreas); in contrast, steatosis and fibroinflammatory disease activity rarely co-occurred in the kidneys or pancreas. This work argues for multi-disciplinary management, already cost-effective in diabetes (46). Prioritisation of modifiable risk factors that mediate liver disease has been shown to be cost-

effective in management of MASLD and poorly controlled type 2 diabetes in some healthcare settings (47), but is infrequently employed (48).

Obesity and hypertension, both widespread in our cohort, provide synergistic risk factors for development and progression of CKD in individuals with type 2 diabetes (49). Detection, early prevention and treatment of CKD is critical to prevent progression to end-stage renal disease.

Reduction in pancreatic fat with weight loss interventions has been observed with improvements in insulin secretion and in glucose homeostasis (19) but we did not observe significant weight change in our cohort over the 7 month follow-up period in routine care. Of interest is the association between poor glycaemic control and pancreatic fibro-inflammation in our study, a finding reproduced recently by Mak et al, in individuals with MASLD from the ANCHOR registry (50). Pancreatic fibro-inflammation may have a more critical role than pancreatic steatosis in established type 2 diabetes.

We noted no significant longitudinal changes in either routine biomarkers and/or imaging over a 7-month follow-up. However, some interesting trends in liver, vascular health and body composition were observed using SGLT2i and GLP-1 RA, with weight loss or with improvement in glycaemic control. In contrast there was no change in such metrics with a conventional glucose lowering therapy approach, or when weight or glycaemic control did not improve. This insight supports the treatment stratification of individuals with type 2 diabetes, according to multi-organ phenotypes (e.g. underlying liver disease and CKD) adopting this technology as a facilitating tool.

We acknowledge some limitations to our study. Future studies, assessing renal size and cardiac structural and functional changes using cardiac MRI may add additional prognostic value. We acknowledge the shorter follow-up interval between successive MRI scans was sub-optimal for sufficient temporal resolution of changes with disease progression or treatment. Imaging datasets, with greater scale, longer duration follow-up, and greater ethnic diversity, may

provide further clarity on the prognostic value of these imaging metrics in obesity- and diabetes-related complications. The impact of individual drug classes on these organ metrics remains unknown and the global multi-organ impact of newer agents, with 'double-digit' weight loss, such as semaglutide and tirzepatide, is of interest.

In summary, using comprehensive, multi-organ, multi-parametric MRI for the first time in individuals living with obesity and type 2 diabetes without previously diagnosed comorbidities, we demonstrate significant evidence of underlying multi-organ dysfunction involving the liver, pancreas, kidneys and cardiovascular system, more pronounced than expected based on age or BMI. Detailed multi-organ imaging would enhance risk and therapeutic stratification of this high-risk group.

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Author Contributions and Guarantor Statement. DJC, HTB, GJK, GT and SA were involved in the conception and design of the study. DJC, GJK, GT, SA, AH and MP were involved in conduct of the study. CD, NE, HTB and DJC were involved in the analysis and CD, PP, HTB and DJC in the interpretation of the results. HTB wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. DJC is the guarantor

of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict-of-interest. CD, PP, and HTB are employees at Perspectum Ltd, the company that developed CoverScan. HTB is also shareholder at Perspectum Ltd. NE and MP are former employees at Perspectum Ltd. MP is a consultant for Perspectum. DC has received funding for conference attendance from Perspectum and has investigator-initiated research grants from NovoNordisk and Astra Zeneca.

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Table 1: Characteristics of the study population, in the whole cohort at baseline and comparison with 134 matched controls and 92 healthy volunteers. Mean and SD or count and percentage are reported. N/a: not available, † = remains significant after additionally controlling for age, sex and ethnicity, * = remains significant after additionally controlling for age, sex, ethnicity and BMI.

	Sample size (n)	**Type 2 Diabetes (n=134)**	**Healthy volunteers (n = 92)**	**P-value: Type 2 diabetes vs. healthy volunteers**	**Matched controls (n=134)**	**P-value: Type 2 diabetes vs. matched controls**
DEMOGRAPHICS						
Age [mean (SD)]	134	61 (11)	44 (12)	**<0.001†**	61 (7)	0.652
Sex (Male) [n (%)]	134	79 (59%)	31 (34%)	**<0.001†**	73 (54%)	0.538
Ethnicity (White) [n (%)]	134	117 (87%)	85 (92%)	0.275	111 (83%)	0.392
Smoking (current) [n (%)]	132	7 (5.3%)	3 (3.3%)	0.531	8 (6.0%)	>0.999
High alcohol consumption [n (%)]	134	7 (5.2%)	N/a	-	16 (12%)	0.079
METABOLIC COMORBIDITIES						
BMI [mean (SD)]	134	31.6 (5.3)	23.4 (3.4)	**<0.001**	31.5 (5.5)	0.754
Categories [n (%)]				**<0.001**		0.874
Lean (< 25kg/m^2)		14 (10%)	68 (74%)		17 (13%)	
Overweight (≥ 25 & < 30kg/m^2)		38 (28%)	21 (23%)		37 (28%)	
Obese (≥ 30 kg/m^2)		82 (61%)	3 (3.3%)		80 (60%)	
Systolic blood pressure (mmHg) [mean (SD)]	133	141 (17)	126 (15)	**<0.001†**	136 (16)	**0.021**
Categories [n (%)]				**<0.001†**		**0.019**
< 140mmHg		64 (48%)	77 (85%)		84 (63%)	
≥ 140mmHg		69 (52%)	14 (15%)		50 (37%)	
Diastolic blood pressure (mmHg) [mean (SD)]	133	79 (9)	79 (11)	0.921	80 (10)	0.66
Categories [n (%)]				>0.999		>0.999
< 90mmHg		114 (86%)	78 (86%)		92 (85%)	
≥ 90mmHg		19 (14%)	13 (14%)		16 (15%)	
HbA1c (%) [mean (SD)]	127	7.92 (1.59)	-	-	5.84 (0.32)	**<0.001**
Categories [n (%)]						**<0.001**
≤ 6%		7 (5.5%)	-	-	85 (66%)	
> 6% & < 6.5%		14 (11%)	-	-	43 (33%)	

	Sample size (n)	Type 2 Diabetes (n=134)	Healthy volunteers (n = 92)	P-value: Type 2 diabetes vs. healthy volunteers	Matched controls (n=134)	P-value: Type 2 diabetes vs. matched controls
≥ 6.5%		106 (83%)	-	-	1 (0.8%)	
HbA1c (mmol/mol) [mean (SD)]	127	63 (17)	-	-	40 (3)	**<0.001**
Categories [n (%)]			-	-		**<0.001**
≤ 42mmol/mol		7 (5.5%)	-	-	84 (65%)	
>42mmol & < 48 mmol/mol		15 (12%)	-	-	44 (34%)	
≥ 48mmol/mol		105 (83%)	-	-	1 (0.8%)	
LIVER MRI METRICS						
cT1 (ms) [mean (SD)]	128	805 (95)	709 (55)	**<0.001***	727 (62)	**<0.001**
Categories [n (%)]				**<0.001***		**<0.001**
< 800ms		66 (52%)	84 (94%)		117 (87%)	
≥ 800ms & < 875ms		33 (26%)	5 (5.6%)		14 (10%)	
≥ 875ms		29 (23%)	0 (0%)		3 (2.2%)	
Liver fat (%) [mean (SD)]	134	11 (8)	2 (2)	**<0.001***	7 (6)	**<0.001**
Categories [n (%)]				**<0.001***		**<0.001**
< 5%		40 (30%)	83 (93%)		74 (55%)	
≥ 5% & < 10%		35 (26%)	5 (5.6%)		33 (25%)	
≥ 10%		59 (44%)	1 (1.1%)		27 (20%)	
Volume (ml) [mean (SD)]	134	1,980 (496)	1,426 (285)	**<0.001***	1,662 (340)	**<0.001**
Categories [n (%)]				**<0.001**		**<0.001**
Normal liver volume		74 (55%)	91 (100%)		126 (94%)	
High liver volume		60 (45%)	0 (0%)		8 (6.0%)	
Advanced MASLD/MetALD (cT1 ≥ 800ms, PDFF ≥ 5%) [n (%)]	128	53 (41%)	0 (0%)	**<0.001**	17 (13%)	**<0.001**
Advanced MASLD (cT1 ≥ 800ms, PDFF ≥ 5% & no/ low alcohol) [n (%)]	128	49 (38%)	0 (0%)	**<0.001**	15 (11%)	**<0.001**
Advanced MetALD (cT1 ≥ 800ms, PDFF ≥ 5% & high alcohol) [n (%)]	134	4 (3.0%)	0 (0%)	**0.148**	2 (1.5%)	0.684
PANCREAS MRI METRICS						
srT1 (ms) [mean (SD)]	99	770 (81)	718 (54)	**<0.001***	740 (77)	**0.004**
Categories [n (%)]				**<0.001***		0.147
< 836ms		79 (80%)	88 (98%)		117 (87%)	
≥ 836ms		20 (20%)	2 (2.2%)		17 (13%)	
Pancreatic fat (%) [mean (SD)]	112	6.5 (4.9)	2.8 (2.3)	**<0.001†**	4.5 (2.7)	**0.004**
Categories [n (%)]				**<0.001†**		0.072

	Sample size (n)	Type 2 Diabetes (n=134)	Healthy volunteers (n = 92)	P-value: Type 2 diabetes vs. healthy volunteers	Matched controls (n=134)	P-value: Type 2 diabetes vs. matched controls
< 4%		42 (37%)	80 (88%)		66 (49%)	
≥ 4%		70 (63%)	11 (12%)		68 (51%)	
Pancreatic disease with steatosis and fibro-inflammation [n (%)]	102	17 (17%)	1 (1.1%)	**<0.001***	10 (8%)	**0.038**
KIDNEY MRI METRICS						
Left cortical T1 (ms) [mean (SD)] ‡	133	1,400 (126)	1,186 (170)	**<0.001†**	N/a	-
Categories [n (%)]				**<0.001**		-
< 1185ms [1.5T] or < 1527ms [3T]		116 (87%)	91 (100%)		-	
≥ 1185ms [1.5T] or ≥ 1527ms [3T]		17 (13%)	0 (0%)		-	
Right cortical T1 (ms) [mean (SD)] ‡	133	1,389 (130)	1,173 (175)	**<0.001**	N/a	-
Categories [n (%)]				**<0.001†**		-
< 1173ms [1.5T] or < 1516ms [3T]		112 (84%)	90 (99%)		-	
≥ 1173ms [1.5T] or ≥ 1516ms [3T]		21 (16%)	1 (1.1%)		-	
Left renal sinus fat volume (ml) [mean (SD)]	121	29 (13)	13 (6)	**<0.001***	N/a	-
Categories [n (%)]				**<0.001***		-
< 26.9ml [male] or < 22.9ml [female]		54 (45%)	78 (96%)		-	
≥ 26.9ml [male] or ≥ 22.9ml [female]		67 (55%)	3 (3.7%)		-	
Right renal sinus fat volume (ml) [mean (SD)]	120	26 (11)	10 (7)	**<0.001***	N/a	-
Categories [n (%)]				**<0.001***		-
< 24.2ml [male] or < 17.9ml [female]		50 (42%)	78 (96%)		-	
≥ 24.2ml [male] or ≥ 17.9ml [female]		70 (58%)	3 (3.7%)		-	
Renal disease with steatosis and fibro-inflammation [n (%)]	132	13 (9.8%)	0 (0%)	**0.001**	N/a	-
AORTIC MRI METRICS						
Abdominal (10^{-3} $mmHg^{-1}$) [mean (SD)]	131	2.8 (1.8)	7.2 (2.9)	**<0.001***	N/a	-
Categories [n (%)]				**<0.001***		-
≥ 3.57 [male] or ≥ 2.85 [female]		41 (31%)	75 (96%)		-	
< 3.57 [male] or < 2.85 [female]		90 (69%)	3 (3.8%)		-	
Ascending (10^{-3} $mmHg^{-1}$) [mean (SD)]	107	2.01 (2.00)	5.16 (2.81)	**<0.001***	N/a	-

	Sample size (n)	Type 2 Diabetes (n=134)	Healthy volunteers (n = 92)	P-value: Type 2 diabetes vs. healthy volunteers	Matched controls (n=134)	P-value: Type 2 diabetes vs. matched controls
Categories [n (%)]				**<0.001**		-
≥ 1.44 [male] or ≥ 0.73 [female]		69 (64%)	73 (96%)		-	
< 1.44 [male] or < 0.73 [female]		38 (36%)	3 (3.9%)		-	
Proximal descending (10^{-3} $mmHg^{-1}$) [mean (SD)]	127	2.05 (1.09)	5.26 (2.08)	**<0.001***	N/a	-
Categories [n (%)]				**<0.001***		-
≥ 2.91 [male] or ≥ 2.11 [female]		32 (25%)	75 (96%)		-	
< 2.91 [male] or < 2.11 [female]		95 (75%)	3 (3.8%)		-	
Abdominal lumen diameter [mean (SD)]	131	21.77 (2.63)	19.69	**<0.001**	N/a	-
Categories [n (%)]						-
< 30mm		131 (100%)	87 (100%)		-	
> 30mm		0 (0%)	0 (0%)		-	
BODY COMPOSITION MRI METRICS						
Visceral adipose tissue (cm^2) [mean (SD)]	134	255 (109)	70 (54)	**<0.001***	N/a	-
Categories [n (%)]				**<0.001***		-
< 217cm^2 [male] or < 138cm^2 [female]		36 (27%)	88 (97%)		-	
≥ 217cm^2 [male] or ≥ 138cm^2 [female]		98 (73%)	3 (3.3%)		-	
Subcutaneous adipose tissue (cm^2) [mean (SD)]	130	278 (126)	153 (87)	**<0.001†**	N/a	-
Categories [n (%)]				**<0.001†**		-
< 238cm^2 [male] or < 349cm^2 [female]		74 (57%)	88 (97%)		-	
≥ 238cm^2 [male] or ≥ 349cm^2 [female]		56 (43%)	3 (3.3%)		-	
ORGAN ABNORMALITY BY MRI						
Liver abnormal [n (%)]	134	103 (77%)	11 (12%)	**<0.001***	60 (45%)	**<0.001**
Pancreas abnormal [n (%)]	109	73 (67%)	12 (13%)	**<0.001***	75 (56%)	0.087
Kidney abnormal [n (%)]	122	90 (74%)	5 (6.2%)	**<0.001***	N/a	-
Body composition abnormal [n (%)]	134	109 (81%)	5 (5.5%)	**<0.001***	N/a	-
Aorta abnormal [n (%)]	125	103 (82%)	5 (6.7%)	**<0.001***	N/a	-
1 Organ abnormal [n (%)]	134	8 (6.0%)	18 (20%)	**0.003***	N/a	-

	Sample size (n)	Type 2 Diabetes (n=134)	Healthy volunteers (n = 92)	P-value: Type 2 diabetes vs. healthy volunteers	Matched controls (n=134)	P-value: Type 2 diabetes vs. matched controls
≥ 1 Organ(s) abnormal [n (%)]	134	134 (100%)	27 (29%)	**<0.001**	N/a	-
≥ 2 Organs abnormal [n (%)]	134	126 (94%)	9 (9.8%)	**<0.001***	N/a	-
≥ 3 Organs abnormal [n (%)]	134	109 (81%)	2 (2.2%)	**<0.001***	N/a	-
≥ 4 Organs abnormal [n (%)]	134	76 (57%)	0 (0%)	**<0.001**	N/a	-
5 Organs abnormal [n (%)]	134	33 (25%)	0 (0%)	**<0.001**	N/a	-

FIGURE LEGENDS

Figure 1: Thirty treatment regimens in 134 individuals with type 2 diabetes under routine care (A) with baseline characteristics suggestive of hypertension and poor glycaemic control (B). Prevalence of individuals with or without elevations in blood pressure and /or HbA1c are shown in pink. Blue: individuals on glucose-lowering treatments that included SGLT2i or GLP1-RA, green: individuals on all other glucose-lowering treatments. Blood pressure and glycaemic control in individuals with established with type 2 diabetes at baseline.

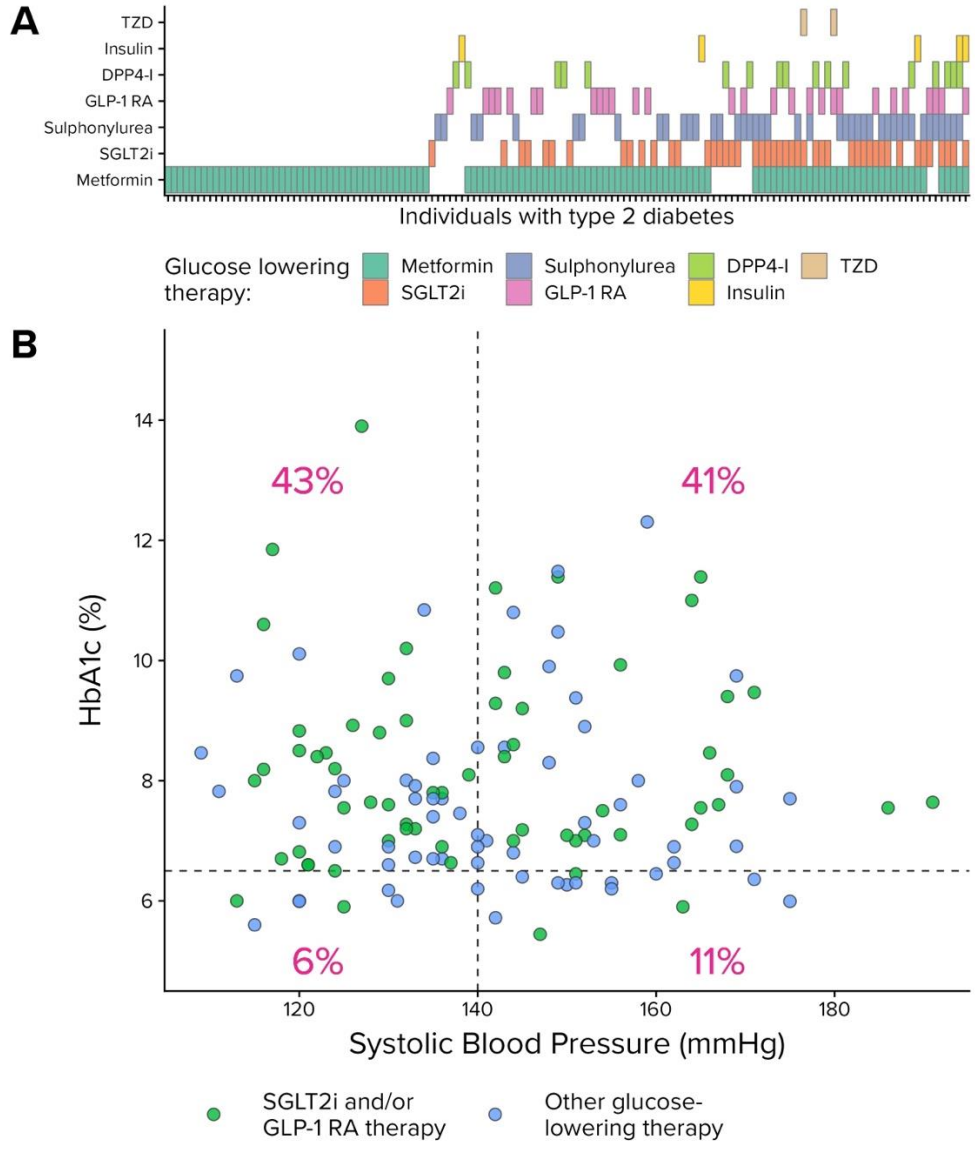

Figure 2: Association of abnormal organ characteristics, based on MRI, with obesity status (A), glycaemic control (B) and duration of type 2 diabetes (C).

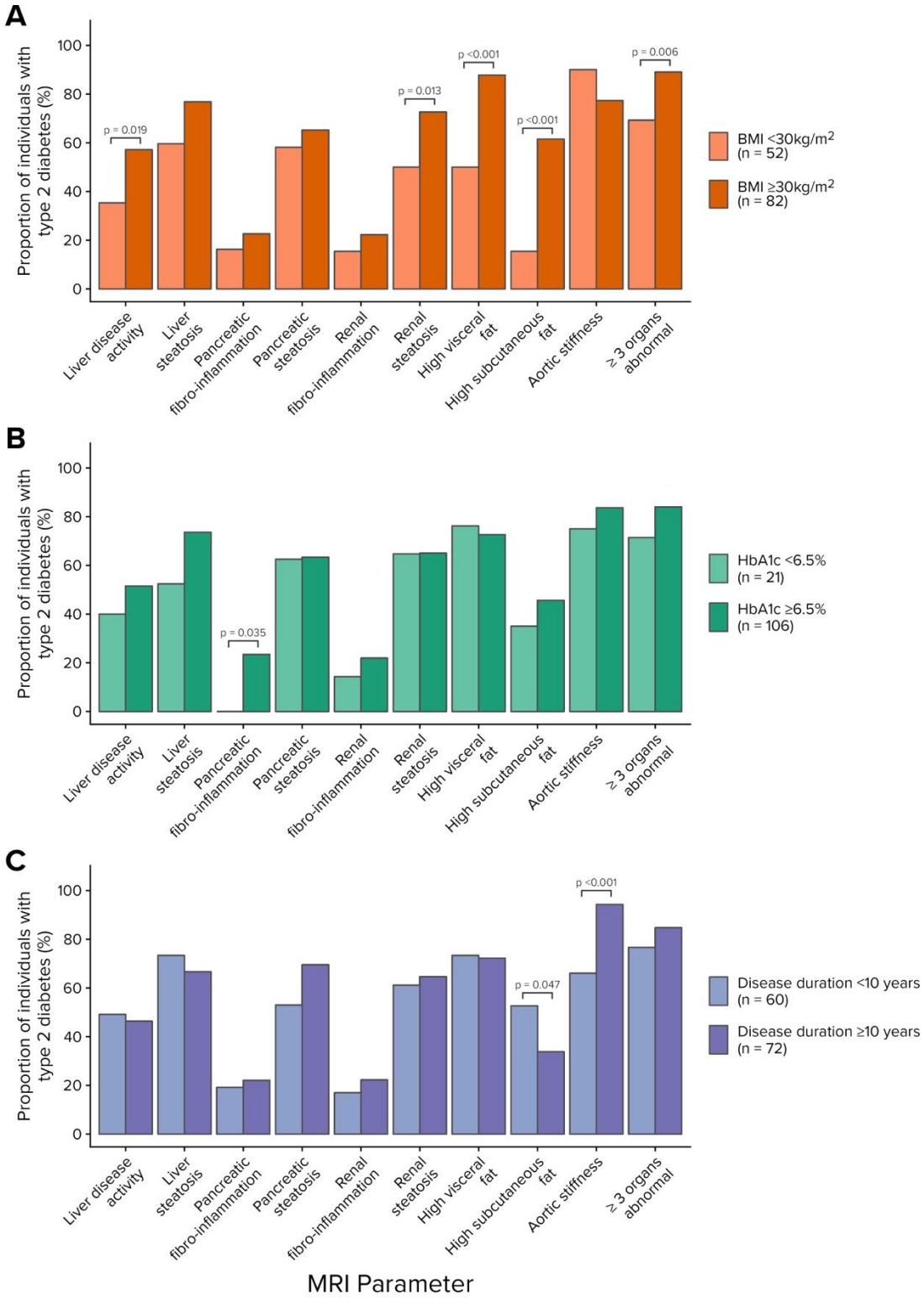

Figure 3: Multiple abnormal organ characteristics in 134 individuals with type 2 diabetes under routine care. A. Abnormalities identified using routine biomarkers. B. Abnormalities identified using MRI. Shown are the numbers of individuals with any of: advanced MASLD/MetALD, pancreas steatosis and/or fibro-inflammation, kidney steatosis and/or fibro-inflammation, aortic stiffness, increased visceral or subcutaneous adipose tissue.

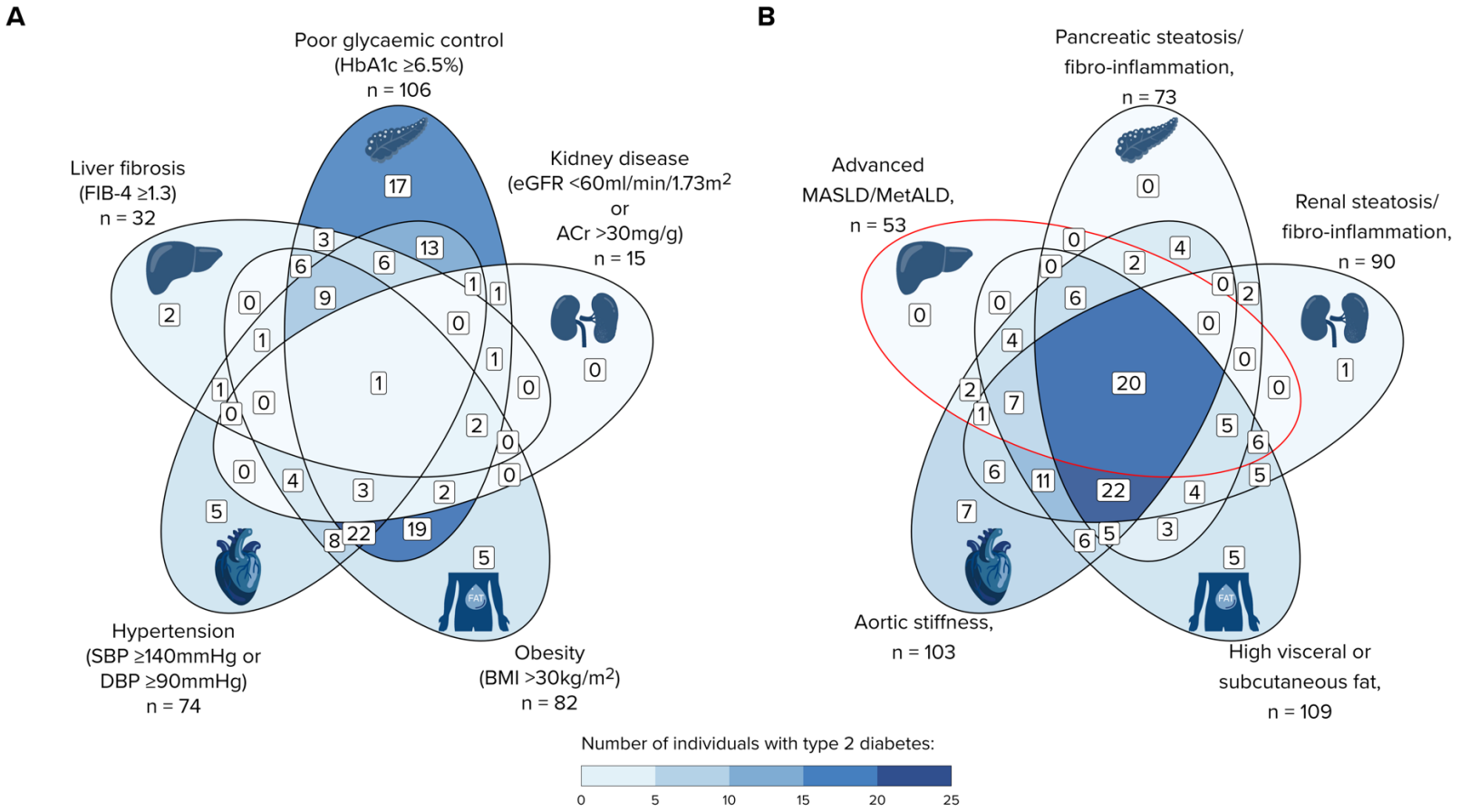

Figure 4: Longitudinal effects in MRI organ metrics over 7 months in individuals with type 2 diabetes achieving at least 5% weight loss (A) or 0.9% reduction in HbA1c (B) or (C) on therapy that included SGLT2i and/or GLP-1 RA compared to those on all other treatments.

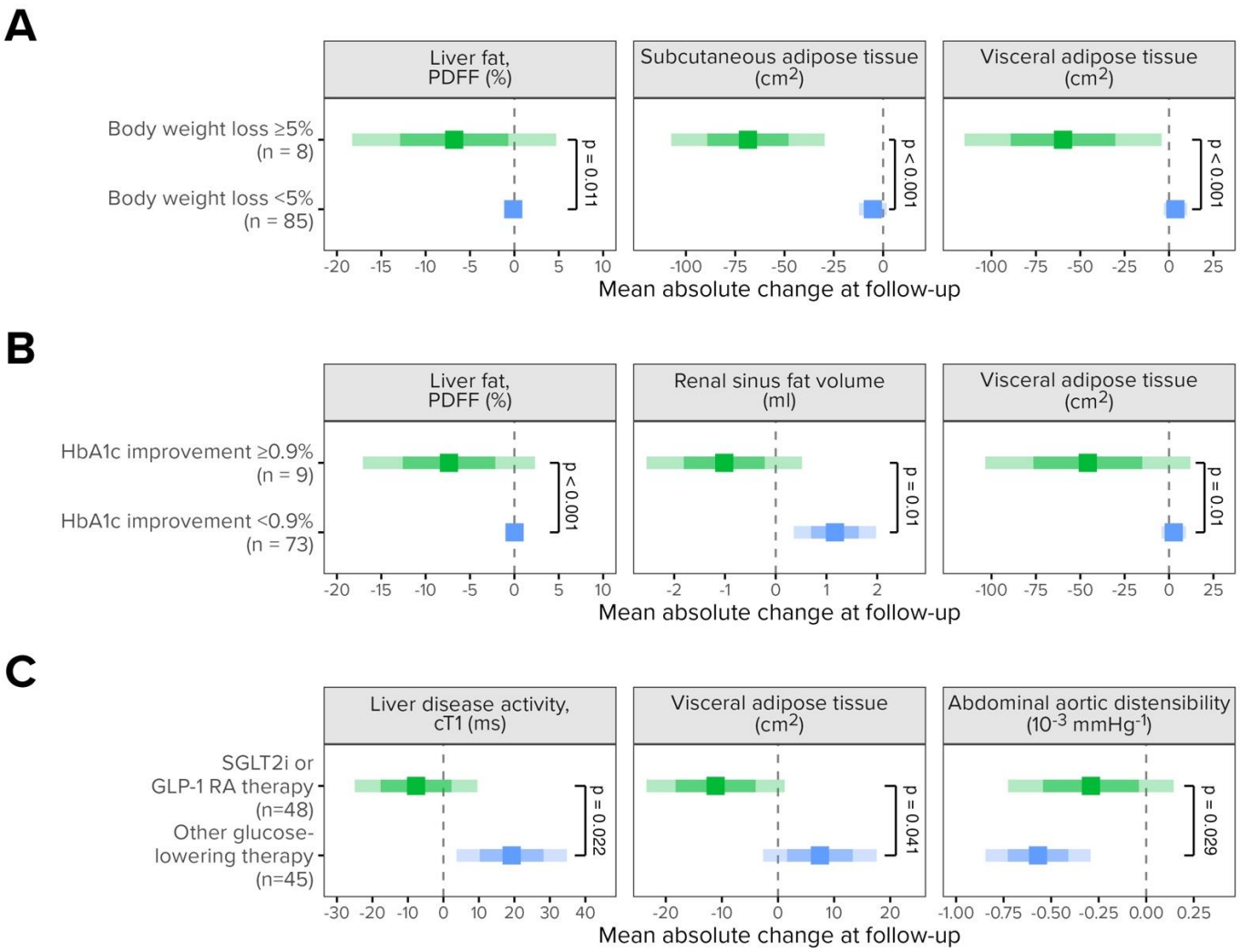

Figure 5: Example multi-organ phenotype in an individual living with type 2 diabetes and obesity, who at baseline was being treated with metformin, sulphonylurea and SGLT2i. Example multi-organ phenotype in an individual living with type 2 diabetes and obesity, who at baseline was being treated with metformin, sulphonylurea and SGLT2i. C-D. Clinically significant reduction in liver disease activity (cT1) over 7 months, despite no weight change. E. Elevated pancreatic fat at baseline, resolved at follow-up. F. Elevation in renal fibro-inflammation (cortical T1) in right kidney, which persisted at follow-up. G. Low aortic distensibility, which persisted at follow-up. H. Elevated VAT and normal SAT, which persisted at follow-up.