

**A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health**

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## **Abstract**

**Non-alcoholic fatty liver disease (NAFLD) is a globally-prevalent health problem, associated in its more severe forms with increased liver-related and cardiovascular-related morbidity and mortality. We established a multidisciplinary metabolic hepatology clinic in 2014 and have analysed the clinical data to evaluate the effectiveness of this service.**

**Patients with NAFLD (n=165) who had attended two or more appointments were included. Pre-specified clinical data were collected prospectively at clinic appointments and analysed retrospectively. Interventions offered included lifestyle advice, commercial weight loss services, pharmacological treatment of diabetes and cardiovascular risk factors.**

**Median follow-up was 13 months (range: 2 – 34). 59% (n=97) of patients had type 2 diabetes mellitus (T2DM). 53% (n=87) underwent liver biopsy of whom 18% (n=16) had cirrhosis. Median alanine aminotransferase (ALT) reduced by 11iu/L ( $p<0.0001$ ), median weight reduced by 3.3kg ( $p=0.0005$ ). There were significant reductions in HbA1c, total cholesterol, NAFLD fibrosis score and liver stiffness. Specifically in patients with T2DM, HbA1c decreased by 4mmol/mol ( $p=0.01$ ) with significant reductions in ALT, weight and total cholesterol. Relative cardiovascular risk assessed by the QRisk3 score reduced in the whole cohort and in those with T2DM. Health economic modelling suggested the clinic intervention among those patients with poorly controlled T2DM was cost-effective.**

**In conclusion, a multidisciplinary approach to the management of patients with NAFLD in this observational cohort study was associated with improvements in liver-related and cardio-metabolic related health parameters and with evidence of cost-effectiveness in patients with poorly controlled T2DM.**

### **Summary Box**

1. What is already known about this subject?

Non-alcoholic fatty liver disease (NAFLD) is a globally prevalent public health burden with the principal causes of morbidity and mortality being from cardiovascular complications as well as liver disease and cancer. A multidisciplinary approach to the management of patients with NAFLD is advocated but there is a paucity of best practice data describing how such services should be shaped and delivered.

2. What are the new findings?

We have evaluated our experience of managing a cohort of patients with NAFLD using a dedicated multidisciplinary approach that is jointly led by hepatologists and diabetologists in a teaching hospital setting with significant input from allied health professionals including diet and lifestyle experts. We describe significant improvements in both clinical and surrogate markers of liver and cardio-metabolic health over a 13-month median follow-up period. These include improvements in liver chemistry and hepatic elastography as well as improvements in weight and glycaemic (diabetes) control.

3. How might it impact on clinical practice in the foreseeable future?

This study forms a useful benchmark of current clinical practice to which other services or interventions may in future be compared. In addition, it may help healthcare providers and health policy makers to refine or design and implement healthcare services related to NAFLD, diabetes and metabolic syndrome.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is a globally prevalent public health burden. Estimates indicate that between 20-30% of many populations are affected and the prevalence is expected to rise with increasing prevalence of obesity and type 2 diabetes (T2DM)(1).

NAFLD is considered a disease spectrum from hepatic steatosis, which may be accompanied by histologically-defined inflammation (non-alcoholic steatohepatitis, NASH), with or without liver fibrosis (typically classified as mild fibrosis (stages: F0-F1), significant fibrosis (F2) or advanced fibrosis (stages: F3-F4) with F4 fibrosis being a diagnosis of cirrhosis)(2). Liver cirrhosis confers a significantly increased risk of hepatic decompensation and development of hepatocellular carcinoma. The presence of advanced fibrosis predicts reduced transplant-free survival, increased liver-related mortality and all-cause mortality(3,4). Nevertheless, the principal causes of morbidity and mortality from NAFLD are from cardiovascular and metabolic complications(3,4). Furthermore, T2DM is the strongest risk factor for NAFLD disease progression(5). Those with both NAFLD and T2DM have accelerated liver disease progression and more prevalent and severe complications of diabetes(6,7). Subsequent studies have suggested that even significant fibrosis is associated with increased mortality(8).

NAFLD may be considered a cardio-metabolic disease as well as a liver disease with implications for risk stratification and for management. Appropriate disease staging at presentation will identify those at high risk of adverse outcomes who would benefit from more intensive management.

As there are no currently licenced treatments specifically for NAFLD, management focuses on modification of risk factors for NAFLD progression and cardiovascular disease within a multidisciplinary framework(9–11). Emphasis is given to weight management and the achievement of meaningful weight loss in those who are overweight or obese via dietary and lifestyle modifications. Medications are used to aid reduction of cardiovascular risk, for example, the use of antihypertensive and statin therapy, as well as to improve diabetes control where appropriate. For the control of diabetes, therapies that are weight-neutral or encourage weight loss such as SGLT2 inhibitors and GLP-1 agonists are favoured(12–15), while newer diabetes therapies also reduce cardiovascular risk(16–18).

This study aimed to evaluate the impact of a metabolic hepatology clinic that adopts a multidisciplinary, holistic approach to treat NAFLD and uses a number of markers of liver and cardio-metabolic health to assess its performance. These included thorough assessment of surrogate markers of liver injury, diabetes control and cardiovascular risk. Furthermore, this study evaluated the effects of the clinic on quality adjusted life expectancy (QALE), and estimated the cost-effectiveness of the approach.

## **Methods**

### Intervention: A multidisciplinary metabolic hepatology clinic

The Oxford University Hospitals NHS Foundation Trust (OUH) delivers a weekly secondary / tertiary multidisciplinary metabolic hepatology clinic, managing patients from across Oxfordshire, UK, and the surrounding regions. Referrals to the clinic are received from both primary care and secondary care settings. OUH works closely with the Oxfordshire Clinical Commissioning Group and has produced guidelines (19) to assist primary care professionals to investigate and refer of patients (this pathway

was updated in November 2017 after the period covered by the analysis in this paper). These guidelines assist GPs to risk stratify patients and help ensure that those at high risk of advanced liver disease are referred to and managed in secondary care. . From January 2015 to November 2017, local guidance recommended that patients with suspected NAFLD in primary care first underwent risk-stratification with the NAFLD fibrosis score with referral of those patients with indeterminate or high risk scores to the Metabolic Hepatology clinic. However, referrals without risk stratification were not refused and risk stratification was performed in clinic. If the diagnosis was unclear, the patients were referred to the General Hepatology clinic. Risk stratification would then be performed by NAFLD Fibrosis Score, Fib4 score and/or FibroScan and subsequent appointments scheduled in the Metabolic Hepatology clinic if appropriate.

The clinic is jointly led by hepatologists and diabetologists/metabolic physicians. The clinic is supported by specialist nurses performing transient elastography (Fibroscan) and anthropometrics immediately prior to the medical consultation and by specialist practitioners via the *Here for Health* Service., This is a special service at OUH that bridges the link between the acute hospital setting and currently available community services. It provides a range of health and wellbeing advice including weight management (diet, lifestyle and exercise), but also smoking cessation, alcohol reduction and signposting to mental health services ([www.ouh.nhs.uk/patient-guide/here-for-health/default.aspx](http://www.ouh.nhs.uk/patient-guide/here-for-health/default.aspx)). Blood testing, imaging, liver biopsy and screening for hepatocellular carcinoma in patients with established cirrhosis are performed where clinically appropriate and in accordance with relevant clinical guidelines. Patients with mild disease, either on non-invasive markers (low-risk NAFLD Fibrosis Score or Fib4, FibroScan <8kPa without adjustable metabolic complication, or liver biopsy F  $\leq$  2 in absence of metabolic complications) are typically discharged from clinic. Exceptions include those with complex metabolic comorbidities, florid NASH in young people and others at the clinician's discretion.

Local guidance since November 2017 recommends repeat non-invasive risk stratification in patients with mild disease in three years to look for evidence of progression.

### Study Analysis

A retrospective analysis of all patients who were managed through the metabolic hepatology clinic at OUH between inception in March 2014 until May 2017 was performed. Patients were included in the analysis if they had (i) attended the clinic at least twice, (ii) had an alanine aminotransferase (ALT) level recorded at baseline and their latest clinic visit, and (iii) had weight recorded at baseline. Clinical data from all patients attending since clinic inception was collected on a clinic proforma and subsequently recorded on a , centrally-held, secure, departmental clinical spreadsheet for audit purposes.

Diagnosis of NAFLD was made according to NICE (20) and other guidance; either radiologically (liver ultrasound or liver magnetic resonance imaging), histologically on liver biopsy, or on the basis of persistently elevated liver enzymes (elevated ALT and/or AST levels ( $> 40\text{IU/L}$ ) in the context of features of the metabolic syndrome and where other causes of liver pathology had been excluded. Patients with known hepatic co-morbidity, patients who did not have a diagnosis of NAFLD, those who had type 1 diabetes and those who had previously undergone or who underwent bariatric surgery during the follow-up period were excluded from the analysis (Supplementary Data: Figure 1).

Patients underwent assessments of liver and cardio-metabolic health using routine non-invasive tools including measurement of serum ALT, AST and liver stiffness measurement by transient elastography (FibroScan), a validated surrogate marker of liver fibrosis (21). Calculation of the Fibrosis-4 (Fib-4) score (22) provided additional non-invasive assessment of risk of advanced liver fibrosis. Liver biopsy,

still the reference standard for diagnosis and assessment of disease severity was performed where clinically indicated.

Cardio-metabolic assessment included measurement of weight, body mass index (BMI), alcohol intake, blood pressure, lipids and diabetes control (HbA1c). All patients were asked to complete a qualitative 7-day food diary in advance of clinic attendance. Cardio-metabolic risk factors were defined using standard measures employed in clinical practice: hypertension if blood pressure was  $\geq 140/90$  mmHg, or if the patient was taking antihypertensive medication; type 2 diabetes according to WHO criteria (HbA1c  $\geq 48$  mmol/mol), if the diagnosis was already established at baseline or if patients were taking anti-diabetic medication; dyslipidaemia according to local thresholds (triglycerides  $> 1.7$  mmol/L and/or high-density lipoprotein (HDL) cholesterol  $< 1.0$  mmol/L (male),  $< 1.3$  mmol/L (female) and obesity if BMI was  $\geq 30$  kg/m<sup>2</sup>. All patients had 10-year cardiovascular risk assessment (absolute and relative risk) calculated retrospectively using the QRISK3-2017 score (23) and each patient's current drug history was recorded at clinic visits. For patients with T2DM, data on prescribed medical therapies was collated from clinic letters and cross-referenced with written clinic proformas.

The primary outcome was change in ALT level between baseline and latest clinic visit. Secondary outcomes were change in weight, glycated haemoglobin (HbA1c), aspartate aminotransferase (AST), lipid profile (total cholesterol, HDL, triglycerides), systolic blood pressure, transient elastography, Fib-4 score, NAFLD fibrosis score (NFS), and QRISK3 cardiovascular risk score. Patients with a missing variable value at baseline and/or latest clinic visit were not included for paired analysis of that variable. A subgroup analysis was performed on patients with (i) T2DM at baseline and (ii) poorly controlled T2DM at baseline, defined as baseline HbA1c  $> 58$  mmol/mol, who also had a latest clinic HbA1c measurement (Supplementary Data: Table 2).

## Economic analysis and assessment of quality adjusted life expectancy

The UKPDS Outcomes Model (version 2.0, UKPDS-OM2), a lifetime simulation model for patients with T2DM which has been extensively validated, was used to model and predict changes in quality adjusted life expectancy (QALE) as well as the potential cost-effectiveness of our approach(24). UKPDS-OM2 was firstly applied to all patients with T2DM and subsequently in those patients with poorly controlled T2DM at baseline (HbA1c > 58 mmol/mol). The model, incorporates phenotypic data and changes to various modifiable cardio-metabolic risk factors over time. A standard, accepted modelling approach was adopted to compare outcomes in the changes observed in those attending the clinic to outcomes in the absence of these changes (see supplementary materials for in depth description).

### **Statistical analysis**

Statistical analysis was performed using GraphPad Prism (version 7.0). Data were non-parametrically distributed as assessed by the D'Agostino-Pearson omnibus test. Continuous variables are quoted as median (range), and categorical variables as numbers and percentages. Non-parametric tests were used to assess for statistical significance (Wilcoxon signed rank test for paired baseline and latest visits, Mann-Whitney U and Chi-square ( $\chi^2$ ) tests for comparing between the T2DM and non-T2DM subgroups) and the threshold for significance was set at the 5%. Endpoints were set as baseline to latest follow-up and response.

### **Results**

#### **Baseline characteristics**

165 patients with NAFLD were followed from baseline until their latest clinic visit. Baseline characteristics are described in Table 1. Median interval between baseline and latest follow-up clinic visit was 13.3 months (range 2–34), with a median of 2 follow-up visits (range 1-5).

Patients reported taking a median of 4 prescription medications (range 0-17) at baseline. Oral hypoglycaemic agents were the most commonly prescribed medication with 52% taking  $\geq 1$  agent, followed by anti-hypertensive therapy (51%) and statin therapy (42%).

87 patients (53%) had a liver biopsy prior to or during the follow-up period (Table 2). There was no significant relationship between T2DM status and histological NAFLD activity scores (NAS) ( $p=0.75$ ). Median NAS in patients with T2DM and without T2DM were both 5. There was also no significant relationship between T2DM status and fibrosis stage ( $p=0.19$ ) although the majority of patients with biopsy-proven cirrhosis in the cohort had T2DM (13/16, 81%).

#### **Changes to liver and cardio-metabolic health: baseline to latest clinic visit in all patients**

At latest follow-up, median ALT had reduced significantly by 11IU/L and median AST reduced significantly by 7IU/L (Table 2 & Figure 1). Median liver transient elastography also reduced significantly by 1.3 kPa. For Fib4 and NFS, there were no changes in the proportion of patients switching between categories (risk of presence or absence of advanced liver fibrosis or indeterminate score) (Fib-4:  $p=0.8$ , NFS:  $p=0.7$ ).

Analysis of weight changes revealed that the majority of patients lost weight. The distribution of weight loss is shown in Figure 1. Figure 1 summarises changes in cardio-metabolic and liver parameters stratified by weight loss. In this retrospective analysis of clinical data, even modest weight

loss of <5% was associated with improvement in these parameters and suggested that the magnitude of improvement was greater with increased weight loss.

QRISK3 10-year cardiovascular relative risk reduced significantly by 0.1 (5%). There was no significant change in QRISK3 10-year absolute risk from baseline to latest visit, though when follow-up age, a component of this algorithm, was corrected to 'age-match' (remain the same) to baseline, this reduced significantly by 0.8 (6%).

Additional analyses of subjects by fibrosis stage (early fibrosis and advanced fibrosis) and by weight response (weight gain or weight loss) were also performed to gain an insight into improvements in liver and metabolic health. These results are summarised in the supplementary data (Supplementary Data Tables 3 and 4).

### **Changes to liver and cardio-metabolic health in patients with Type 2 Diabetes (T2DM)**

T2DM is strongly associated with disease progression (5), and therefore a subgroup analysis of patients with T2DM was performed (Tables 1 & 2).

At baseline, patients with T2DM were older than patients without T2DM ( $P<0.0001$ ) and as expected had higher baseline HbA1c ( $P<0.0001$ ) (Table 1). Liver stiffness was also significantly higher at baseline in those with T2DM ( $p=0.011$ ). There was a significant relationship between the presence of T2DM and total number of metabolic syndrome components ( $p<0.0001$ ). Those with T2DM had lower total cholesterol at baseline than those without ( $p=0.0011$ ) (Table 1). Statin use at baseline was higher in those with T2DM (65%) compared to those without T2DM (42%).

Median HbA1c reduced significantly by 4mmol/mol between baseline to last follow-up in those patients with T2DM (Table 2). Improvement was most marked in patients who had poorly controlled T2DM at baseline (HbA1c > 58 mmol/mol,  $n=43$ ), reducing by 14 mmol/mol (Supplementary Data:

Table 2). There were also significant improvements in categories of glycaemic control for those with poorly controlled T2DM subgroup ( $p = 0.0006$ ) (Figure 2). Weight also decreased in patients with T2DM (Table 2).

At baseline, 85 (88%) of patients with T2DM were already prescribed oral glucose lowering therapy, 26% were prescribed insulin therapy and 5% were prescribed GLP-1 therapy. 21% of patients with T2DM started GLP-1 therapy over the duration of the study and 20% of patients who were on insulin therapy at baseline had this discontinued. In those who had insulin therapy discontinued ( $n=5$ ), median HbA1c reduced by 13mmol/mol from this point to latest follow-up. 15% of patients were commenced on statin therapy. Net changes to medications in patients with T2DM are summarised in Supplementary Data: Figure 2.

### **Changes in quality adjusted life expectancy (QALE) and Economic Analysis in patients with T2DM**

For all patients with T2DM, the UKPDS OM2 model estimated no significant difference in mean life expectancy in the intervention group (clinic attendees) compared to the reference group (baseline measures carried forward), (Supplementary Data: Table 1). In those with poorly controlled T2DM, the intervention group had a significantly increased mean life expectancy of 24 days (95% CI: +2 to +50 days) compared to the reference group. Similarly, mean QALE was significantly increased by 29 days (95% CI: +6 to +55 days) suggesting that patients with poorly controlled T2DM managed through our multidisciplinary clinic approach had significant improvements in both overall and quality adjusted life expectancy.

UKPDS-OM2 was also used to evaluate cost-effectiveness in patients with poorly controlled T2DM. Lifetime (total) costs were £30.0k in the clinic group and £29.5k in the reference group who did not attend the clinic, a mean difference of £0.5k. Lifetime QALYs were 11 years in the clinic group and 10.9 years in the reference group, a difference of 0.1 years (29 days). The resulting incremental cost-

effectiveness ratio (ICER, cost per quality-adjusted life year (QALY) was £6.1k (95%CI: £0.3k - £59.3k) with 91% of model bootstraps runs falling below a cost per QALY threshold of £20,000.

## **Discussion**

Recent UK and European guidelines (20,25), advise that management of NAFLD should be multifaceted and patients should be managed using a multidisciplinary approach(9,10). Nevertheless, there is still a paucity of best practice data describing how such services should be shaped and delivered as well as objective evaluations of the impacts of a multidisciplinary approach on patient outcomes.

Here, we have evaluated our experience of managing a cohort of patients with NAFLD using a dedicated multidisciplinary approach that is jointly led by hepatologists and diabetologists in a teaching hospital setting. We describe significant improvements in both clinical and surrogate markers of liver and cardio-metabolic health over a 13-month median follow-up period. This is an observational study of real-life clinical data making it applicable to clinical practice. There was, however, no control arm and the intervention is not uniform for the cohort given the personalised nature of the clinical approach, so causality cannot be inferred. Moreover, such data may be confounded by selection bias and regression to the mean. Nevertheless, it forms a useful benchmark of current clinical practice to which other services or interventions may be compared.

### **Improvements in markers of liver health**

We observed a 14% reduction in liver stiffness in patients attending the metabolic hepatology clinic, measured at point of care, and an associated 21% improvement in serum ALT, an insensitive marker

of NASH, though one which is still commonly used by healthcare professionals(26,27). This improvement in ALT is similar to that observed in patients with NAFLD managed through a similar multidisciplinary approach(9) and in lifestyle intervention trials(28). ALT has also been highlighted as a non-invasive surrogate marker of response in clinical trials in NAFLD/NASH(29). No other current non-invasive biomarkers, serological or non-serological, have been validated to monitor changes in liver disease severity or to predict liver-related health outcomes, mainly due to poor sensitivity to detect small changes in liver fibrosis(5). In this cohort, there was no significant improvement in the Fib-4 score. There were also no significant changes in the numbers of patients predicted to have advanced liver fibrosis between baseline and follow-up using non-invasive scores, though the relevance or utility of these findings is not known.

### **Weight Loss and glycaemic control**

Both UK NICE(30) and American Diabetes Association (ADA) (31) guidance highlight the importance of ‘personalised’ or ‘individualised’ care when managing patients’ diabetes taking into account comorbidities and include guidance on weight management. In particular, the more recent ADA guidance outlines that clinicians should consider the weight and cardiovascular risk effects of glucose lowering therapies when escalating diabetes therapy which is particularly important as some newer agents such as GLP-1 agonists and SGLT2 have been to have beneficial effects on either or both of weight and cardiovascular risk.

In the UK, GLP-1 therapy has a licence for use in patients with T2DM and NICE guidance(30) outlines that this therapy is recommended in patients with poorly controlled T2DM and who are obese, owing to improvements to glycaemic control and promotion of weight loss. This analysis indicates a reduction in prescriptions for diabetes medications, such as insulin, that are associated with weight

gain and an increase in prescriptions for diabetes medications that are weight neutral or associated with weight loss and those which potentially confer cardiovascular protection. These findings were complemented by overall improvement in glycaemic control for all patients with T2DM, with improvement most marked in those with poorly controlled T2DM. These findings on improvement in glycaemic control in a real life clinic setting are consistent with previously published studies investigating the impact of diet and or exercise in patients with T2DM. For example, in the Early ACTID trial in patients with recently diagnosed T2DM who had good glycaemic control at baseline (mean baseline HbA1c 6.64–6.72%), HbA1c improved by around 3.3mmol/mol at 6 and 12 months in those provided with 'dietary support' (dietary consultation every 3 months with monthly nurse support) compared with a control group provided with 'usual care' (initial dietary consultation and follow-up every 6 months – which is often the standard model and frequency of care for patients managed in primary care). (32) Additionally, in this study there was no difference in improvement in HbA1c between the 'dietary support' group and a 'diet plus activity' group (as per diet group, plus 30 min brisk walking five times per week) at either 6 or 12 months. Previous studies have however shown that a combination of diet and exercise is effective in improving glycaemic control by around 11mmol/mol at 6 and 12 months.(33) Similarly, in another study patients with T2DM either provided with specifically tailored food for 1 year or with monthly individual dietary counselling advice saw an approximate 11mmol/mol reduction in HbA1c over 12 months whilst a control group receiving standard diabetes care monthly via appointment with a doctor or nurse saw no change in HbA1c over 12 months.(34,35) Improvement in glycaemic control in the scale observed in our study are accepted as likely to improve both diabetes-related and liver-related complications.

Overall, patients achieved a median 3.4% weight loss, though there was considerable variation in response. 23% of patients (37/159 with both baseline and latest weight measurements recorded) lost at least 5% of their baseline weight by latest visit. Previous studies have demonstrated an association

between weight loss and improvements in NAFLD, with a reduction in excess of 3-5% thought to be required for improvement of hepatic steatosis and / or NASH (36,37). Stratification of markers of liver and cardio-metabolic health by weight response demonstrated that improvements to these markers appear to correlate with degree of weight loss. Our data also suggests that even modest weight loss is associated with improvements in markers of liver and cardio-metabolic health.

Patients often struggle to lose and maintain weight loss without structured support, but there is evidence that commercial weight loss programmes have significant benefit (38) with weight loss of >5% reported, which is of a magnitude that will confer benefit to patients with NAFLD. Liraglutide at a higher dose of 3mg daily is also licenced for use in patients with obesity without diabetes, but its use in this context is not yet supported through NICE guidance within the NHS.

Finally, our simulation of the lifetime costs and outcomes of the clinic intervention in patients with poorly controlled T2DM indicated that it had a high probability of being cost-effective at the thresholds used by NICE, with an incremental cost per QALY of £6.1k. Whilst there was no dedicated control group available, the standardised modelling approach was adopted. As such, these findings provide useful additional information and have importance due to the high and growing burden of NAFLD and the need for health authorities to have both effective, yet cost-effective strategies at their disposal when working within confined financial envelopes.

## **Conclusions**

While considerable effort is going into the development of novel therapies that target the hepatic manifestations of NAFLD/NASH, data from this study indicate that significant improvements in surrogate markers of liver and cardio-metabolic disease can be achieved through effective

implementation of existing risk stratification and treatment strategies. Furthermore, given that NAFLD is both a liver and a cardio-metabolic disease, we have shown that adopting a multidisciplinary approach to its management, involving not only hepatologists, diabetologists and metabolic physicians, but also allied health professionals including diet and lifestyle experts, is an effective and potentially cost-effective way to manage these complex patients.

**Table 1. Baseline characteristics of the total cohort and by T2DM status.**

Baseline characteristic, median (range) or number (%)	Total cohort n = 165	T2DM subgroup n = 97	Non-T2DM subgroup n = 68
<b>Demographic</b>			
Age, years	53 (16-79)	57 (29-79)	47.5 (16-69)
Sex, male	106 (64.2%)	62 (63.9%)	44 (64.7%)
Caucasian ethnicity	132 (80.0%)	78 (80.4%)	54 (79.4%)
<b>Metabolic</b>			
<sup>‡</sup> HbA <sub>1c</sub> , mmol/mol	46 (25-124)	59 (35-124)	36.5 (25-46)
<sup>  </sup> Total cholesterol, mmol/L	4.4 (2.4-9.0)	4.0 (2.4-7.7)	4.9 (2.7-9.0)
<sup>  </sup> HDL, mmol/L	1.0 (0.5-2.4)	1.0 (0.5-1.7)	1.0 (0.8-2.4)
<sup>◊</sup> Triglyceride, mmol/L	1.93 (0.52-17.01)	2.13 (0.52-10.71)	1.72 (0.68-17.01)
<sup>§</sup> Systolic blood pressure, mmHg	140 (105-190)	140 (105-189)	138 (108-190)
<b>Metabolic syndrome (MetS)</b>			
BMI, kg/m <sup>2</sup>	33.3 (23.9-72.1)	34.0 (23.9-52.6)	32.5 (24.2-72.1)
Obesity (BMI>30kg/m <sup>2</sup> )	120 (72.7%)	71 (73.2%)	49 (72.1%)
Hypertension	93 (56.4%)	72 (74.2%)	21 (30.9%)
Dyslipidaemia	105 (63.6%)	71 (73.2%)	34 (50.0%)
Number of MetS components, /4	3 (0-4)	3 (1-4)	2 (0-3)
<b>Lifestyle</b>			
Alcohol, units/week	0 (0-21)	0 (0-21)	0 (0-20)
Current Smoker	10 (6.1%)	6 (6.2%)	4 (5.9%)
Ex-smoker	53 (32.1%)	35 (36.1%)	18 (26.5%)
<b>Liver</b>			
ALT, IU/L	52 (12-215)	50 (12-200)	54 (12-215)
Abnormal ALT (> 40 IU/L)	111 (67.3%)	60 (61.9%)	51 (75.0%)
<sup>↑</sup> Transient elastography, kPa	9.2 (3.5-75.0)	10.1 (4.3-75.0)	8.2 (3.5-53.3)
<b>Biopsy characteristics</b>			
Number (%)	87 (52.7%)	54 (55.7%)	33 (48.5%)
*NAS, /8	5 (2-8)	5 (2-8)	5 (2-7)
*NASH	57 (72.1%)	36 (73.5%)	21 (70.0%)
**Fibrosis stage, (F0-F4)	2 (0-4)	3 (0-4)	2 (1-4)
F0	1 (1.2%)	1 (1.9%) 2 (50.0%)	0 (0%)
F1	15 (17.2%)	6 (11.1%)	9 (27.3%)
F2	34 (39.1%)	20 (37.0%)	14 (42.4%)
Bridging fibrosis (F3)	21 (24.1%)	14 (25.9%)	7 (21.2%)
Cirrhosis (F4)	16 (18.4%)	13 (24.1%)	3 (9.1%)

<sup>‡</sup> number of patients with baseline measurement, n=136, 88, 48 (of total cohort, T2DM subgroup, non-T2DM subgroup, respectively); <sup>||</sup> n=113, 68, 45; <sup>◊</sup> n=100, 59, 41; <sup>§</sup> n=137, 82, 55; <sup>↑</sup> n=133, 73, 60.

Biopsy Characteristics provided for available data \* NAS (NAFLD activity score) (/8); NASH defined as NAS ≥ 5; Number of patients with measurement per group (percentage with NASH): n=79, 49, 30 in each column group. \*\* Fibrosis stage (Brunt's scale) (F0-F4); Cirrhosis defined as fibrosis stage F4 or historical diagnosis in the case of 1 missing biopsy score. Number of patients with measurement per group (percentage): n=86, 53, 33.

**Table 2. Change in liver and cardio-metabolic health parameters from baseline to latest visit.**

Measure (median)	Total cohort					T2DM subgroup				
	N	Base.	Latest	Δ	P value	N	Base.	Latest	Δ	P value
<b>Liver function test</b>										
ALT, IU/L	165	52 (12-215)	41 (11-240)	-11	<b>&lt;0.0001</b>	97	50 (12-200)	40 (11-125)	-10.0	<b>&lt;0.0001</b>
AST, IU/L	65	40 (15-171)	33 (14-105)	-7	<b>0.011</b>	35	35 (16-171)	31 (14-63)	-4.0	0.13
<b>Weight</b>										
Weight, kg	159	97.3 (55.0-206.0)	94.0 (53.9-182.2)	-3.3	<b>0.0005</b>	94	96.8 (55.0-154.6)	94.6 (53.9-180.5)	-2.2	<b>0.0030</b>
<b>Metabolic</b>										
HbA <sub>1c</sub> , mmol/mol	112	49 (25-124)	47 (22-110)	-1.5	<b>0.0045</b>	84	59 (35-124)	55 (33-110)	-4.0	<b>0.011</b>
Total cholesterol, mmol/L	76	4.7 (2.4-9.0)	4.0 (1.9-8.1)	-0.7	<b>0.0023</b>	48	4.1 (2.4-7.7)	3.9 (1.9-8.1)	-0.20	<b>0.0071</b>
HDL, mmol/L	76	1.0 (0.5-2.4)	1.0 (0.6-1.9)	0.0	0.75	48	1.0 (0.5-1.7)	1.0 (0.6-1.9)	0.00	0.85
Triglyceride, mmol/L	47	2.1 (0.67-17.0)	1.9 (0.6-9.0)	-0.25	0.28	29	2.1 (0.7-7.8)	2.0 (0.6-9.0)	-0.12	0.36
Systolic blood pressure, mm Hg	125	140 (105-189)	135 (102-193)	-5	0.24	74	141 (105-189)	136 (102-193)	-5	0.76
<b>Liver</b>										
Fib-4 score	62	1.1 (0.2-7.3)	1.2 (0.2-9.3)	0.05	0.71	35	1.5 (0.4-7.3)	1.2 (0.4-9.3)	-0.28	0.94
NFS	59	-1.0 (-6.5-+5.8)	-0.69 (-6.0-+3.9)	0.32	<b>0.0012</b>	33	0.02 (-3.9-3.0)	-0.3 (-4.7-3.1)	-0.33	0.089
Transient elastography, kPa	73	9.1 (3.5-75)	7.8 (3.2-57)	-1.3	<b>0.0097</b>	39	9.7 (4.3-75)	8.4 (4.4-57)	-1.3	0.067
<b>CVD (QRISK3)</b>										
Absolute risk, %	159	12.5 (0.1-60.9)	12.7 (0.1-52.6)	0.2	0.17	94	18.3 (1.7-61.0)	19.3 (1.9-53.0)	1.0	0.13
Relative risk	159	2.1 (0.7-11.5)	2.0 (0.8-12.9)	-0.1	<b>0.0001</b>	94	2.7 (1.1-11.5)	2.6 (1.1-12.9)	-0.15	<b>0.0006</b>

N, number of patients with paired data; Δ, difference between median at baseline (base.) and latest visit;

**Figure Legends:**

Figure 1: Change in weight and change in cardio-metabolic and liver health stratified by weight loss: baseline to follow-up

Figure 2: Change in HbA1c in patients with Type 2 Diabetes Mellitus (T2DM): baseline to follow-up

### **Contributorship Statement**

**JFC, AM and JWT planned and designed the study and take overall responsibility for the content. JFC and JWT jointly lead the metabolic hepatology clinical service at OUH NHS Trust described in the manuscript and along with AM, MP, JDR and MA provide clinical care to subjects attending this service. AM, KM, MA, TM and AS collated the clinical data analysed. AM and KM undertook the primary data analysis. AM, KM, RH and AG designed and undertook the health economic analysis. AM, KM, JWT and JFC wrote the manuscript which all authors subsequently reviewed and contributed to.**

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