Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

Intervention Description: 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. The clinic is jointly led by hepatologists and diabetologists/metabolic physicians and 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 health promotion service at OUH that bridges the link between the acute hospital setting and currently available community services. *Here for Health* has two main functions; firstly, providing lifestyle advice regarding healthy eating, exercise, alcohol use, smoking cessation and mental health support and secondly, signposting and referral to community-based health promotion services including tier 2-3 weight loss services, drug and alcohol services and mental health counselling services.

Follow-up for patients in the Metabolic Hepatology clinic is based on patient need. If a patient undergoes risk stratification and is found to have mild disease and can be managed well in primary care, they are discharged with advice on repeat community-based risk stratification at 2-3 years and re-referral if required. Those patients receiving diagnostic procedures such as liver biopsy or significant therapeutic intervention (lifestyle or medical) are typically offered follow-up at 3-6 months depending on individual patient needs. For those with stable advanced fibrotic liver disease (F3) but who are not cirrhotic, annual follow-up is arranged. For those with compensated NASH cirrhosis, follow-up is routinely at six monthly intervals.

All patients are seen by a specialist clinic nurse (for anthropometry and Fibroscan if required) and a hepatologist at each appointment, with a diabetologist seeing most patients with diabetes and all patients with poorly controlled diabetes. All patients are offered a *Here for Health* review at their initial visit, and if further issues arise, at subsequent visits. Additionally, *Here for Health* offers an open-access walk-in service if patients wish to attend at an alternative time.

Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

Supplementary Data Table 1. Change in liver and cardio-metabolic health parameters from baseline to latest visit stratified by fibrosis stage (early and advanced fibrosis)

Measure Median (range)	Fibrosis Stage F0-F2 (Early Fibrosis)					Fibrosis Stage F3-F4 (Advanced Fibrosis)				
	N	Base.	Latest	Δ	*P* value	N	Base.	Latest	Δ	*P* value
Liver										
ALT, IU/L	50	66 (12-215)	48 (15-240)	-18	**0.0005**	37	50 (15-200)	40 (14-114)	-10	**0.014**
Transient elastography, kPa	30	8.4 (4.3-17.3)	7.3 (4.3-20)	-1.1	**0.009**	14	17.6 (6.8-75.0)	13.0 (6.1-57.0)	-4.6	0.22
Weight										
Weight, kg	48	97.7 (58.3-154.6)	96.8 (56.9-182.2)	-0.9	0.7	36	98.2 (70.0-159.5)	93.2 (71.9-166)	-5.0	**0.020**
Metabolic										
HbA_{1c}, mmol/mol	32	49 (34-124)	46 (30-110)	-3	0.27	28	48 (32-93)	47 (33-91)	-1	0.60
Total cholesterol, mmol/L	27	5.1 (2.50-9.0)	4.7 (2.70-8.1)	-0.4	0.33	20	4.0 (2.4-7.1)	3.7 (1.9-7.3)	-0.3	0.052
HDL, mmol/L	27	1.0 (0.5-1.7)	1.0 (0.6-1.9)	0.0	0.75	20	1.0 (0.7-2.4)	1 (0.7-1.9)	0	0.55
CVD (QRISK3)										
Absolute risk, %	48	10.7 (0.1-42.1)	9.6 (0.1-37.8)	-1.1	0.53	36	16.0 (0.2-60.9)	15.4 (0.1-52.6)	-0.6	0.27
Relative risk	48	2.5 (0.8-11.5)	2.3 (0.9-12.9)	-0.2	0.13	36	2.3 (1.0-11.1)	2.2 (0.8-6.6)	-0.1	**0.0092**

N, number of patients with paired data; Δ, difference between median at baseline (base.) and latest visit;
Wilcoxon signed rank test between baseline and latest; bold *P* value represents statistical significance.

Supplementary Data Table 2. Comparison of baseline parameters in those who gained weight and those who lost weight between baseline and follow-up

Baseline Parameter Median (range)	Weight Gain	Weight Loss*	P value
n	58	101	
ALT, IU/L	55 (12-174))	51 (14-215)	1.0
n	38	70	
HbA1c, mmol/mol	45 (31-124)	53 (25-103)	0.16
n	30	44	
Tchol, mmol/L	4.7 (2.7-6.5)	4.5 (2.4-7.7)	0.85
n	58	101	
CVD QRISK3 Relatve Risk	2.3 (0.8-11.1)	2.1 (0.7-11.5)	0.15
n	27	44	
Liver Stiffness, kPa	9.5 (4-75)	8.5 (3.5-36.3)	0.51

*or no change

n, number of patients with paired data;
Wilcoxon signed rank test between baseline and latest; bold *P* value represents statistical significance.

Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

Supplementary Data: Table 3. Change in metabolic and liver health variables from baseline to latest visit for the poorly controlled T2DM subgroup.

Variable Median (range)	**N**	**Baseline visit**	**Latest visit**	**Δ**	***P* value**
Liver function test					
ALT, U/L	43	47 (21-189)	39 (11-98)	-8	**<0.0001**
AST, U/L	14	40 (21-171)	33 (24-84)	-7	0.1776
Weight					
Weight, kg	43	98.1 (55.0-143.7)	95.1 (53.9-180.5)	-3.0	**0.0002**
Metabolic					
HbA_{1c}, mmol/mol	43	76 (59-124)	62 (40-110)	-14	**<0.0001**
Total cholesterol, mmol/L	26	4.6 (2.7-7.7)	4.0 (1.9-8.1)	-0.6	**0.0012**
HDL, mmol/L	26	1.1 (0.5-1.7)	1.0 (0.60-1.6)	-0.1	0.8244
Triglyceride, mmol/L	18	3.27 (0.92-7.79)	2.34 (1.34 -8.98)	-0.93	0.2121
Systolic blood pressure, mmHg	37	141 (105-189)	133 (102-181)	-8.00	0.2802
Liver					
Fib-4 score	15	2.23 (0.52-7.26)	1.23 (0.42-9.26)	-1.00	0.7933
NFS	13	0.24 (-2.54-3.04)	-0.31 (-1.83-3.08)	-0.55	0.6975
Transient elastography, kPa	22	10.45 (4.4-36.3)	8.95 (4.4-30.4)	-1.5	0.0805
***CVD** (QRISK3)*					
Absolute Risk, %	41	17.8 (2.1-60.9)	18.6 (3.0-52.6)	0.8	0.9100
Relative Risk	41	2.7 (1.3-11.1)	2.6 (1.1-9.5)	-0.1	0.4390

Abbreviations: N, number of patients with paired data; Δ, difference between median at baseline and latest visit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; CVD, cardiovascular disease.

Wilcoxon signed rank test between baseline and latest visit; bold *P* value represents statistical significance.

Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

Supplementary Data: Table 4.

Economic analysis of patients with T2DM using UKPDS Outcomes Model v0.2**

	Clinic Group		Reference Group		Difference	
	Average	**95% CI**	**Average**	**95% CI**	**Average**	**95% CI**
Mean Life Expectancy	years		years		days	
All with T2DM	14.0	13.7-14.3	14.0	13.8-14.3	-9.8	-23.4-+1.4
Poorly controlled T2DM	14.0	13.8-14.3	13.9	13.7-14.2	23.8	1.9-50.3
Quality Adjusted Life Expectancy	years		years		Days	
All with T2DM	11.1	10.9-11.3	11.1	10.9-11.3	-6.1	-18.2-+4.4
Poorly controlled T2DM	11.0	10.9-11.3	10.9	10.8-11.2	28.9	6.4-55.1
Therapy Costs, £						
All with T2DM	570	569-570	-	-	-	-
Poorly controlled T2DM	570	569-570	-	-	-	-
Complication costs, £k						
All with T2DM	30.3	29.4-31.5	30.2	29.5-31.3	0.03	-0.22-+0.38
Poorly controlled T2DM	29.4	28.4-30.8	29.5	28.7-30.5	-0.09	-0.53-+0.67
Total cost, £k						
All with T2DM	30.8	30.0-32.0	30.2	29.5-31.3	0.60	0.35-0.95
Poorly controlled T2DM	30.0	29.0-31.4	29.5	28.7-30.5	0.48	0.046-1.2
ICER (Cost per QALY), £k						
All with T2DM	-	-	-	-	-	-
Poorly controlled T2DM	6.1	0.3-59.3*	-	-	-	-

T2DM Cohort: n=97; Poorly Controlled T2DM Cohort: n=43

Clinic values held constant from year 3 onwards (group 1) vs. baseline values held constant from year 0 (group 2).

Model parameters: 1 year of therapy at £591. 20,000 loops with 250 bootstraps run 5 times. Discount rate 3.5.

*Percentage of bootstraps below Cost per QALY value of £20,000 = 91.2%.

**Economic analysis and assessment of quality adjusted life expectancy using the UKPDS Outcomes Model:

The UKPDS Outcomes Model (version 2.0, UKPDS-OM2) has been extensively validated for patients with T2DM and was used to model and predict changes in quality adjusted life expectancy (QALE) as well as the cost-effectiveness of the approach (23). This was applied to all patients with

Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

T2DM (baseline HbA1c > 48 mmol/mol), and subsequently in those patients with poorly controlled T2DM at baseline (HbA1c > 58 mmol/mol). The design of the model and analysis adhered to standard good practice guidelines, such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp) which has been widely adopted, though as this is not a stand-alone economic evaluation but an additional analysis within the wider paper, not every point could be followed.

The UKPDS Outcome Model incorporates changes to various modifiable and non-modifiable cardio-metabolic risk factors. The effects of changes to these parameters in patients with T2DM attending our clinic (intervention group) was measured and compared to a reference group where baseline modifiable risk factors for each patient attending our clinic were held constant (reference group) during the running of the UKPDS model (70 years or death). For the intervention group, the modifiable risk factors of each patient were held constant from the point of latest follow-up to death or year 70 of the model.

Missing baseline data for patients were populated using the mean baseline value of each group of interest. Missing data at subsequent years for the group of interest were populated with the patients' own values from the previous year carried forward.

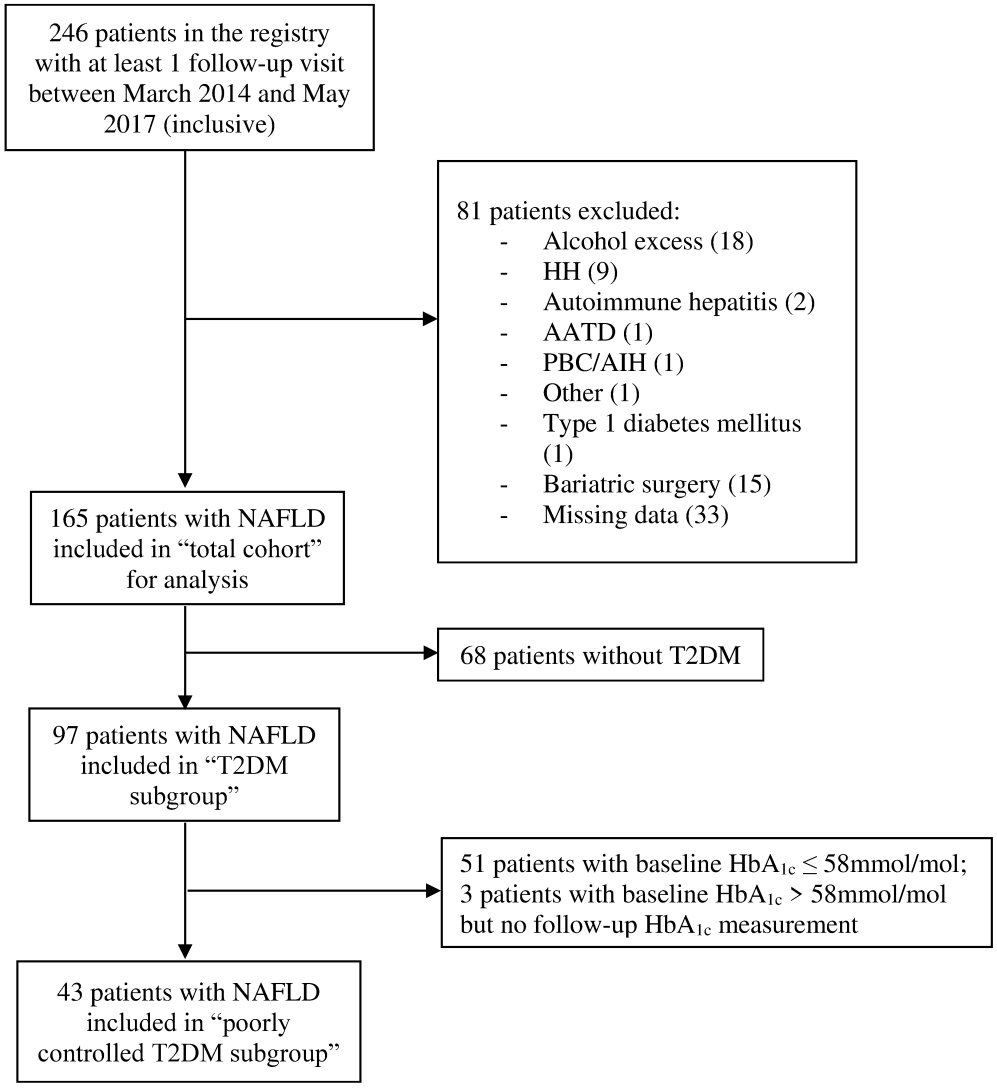
Costs were based on 2016-17 price levels. 1 year of therapy based on the mean and median follow-up period of 1 year was assumed and costed at £591 based on 1 new consultation (Spec Code 306, Hepatology, POD OPFAMPCL: £285) and 2 follow-up consultations (Spec Code 306, Hepatology, POD OPFUPMPCL £153 each), as per 2016-17 NHS National Tariffs reimbursed to OUH. Complication costs were based on default values incorporated in the UKPDS Outcomes Model version 2.

Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

Each model scenario was run 5 times using 20,000 loops (averaging across repeated simulations to minimise monte carlo variation) and 250 bootstraps (to derive 95% confidence intervals reflecting model parameter uncertainty). Mean differences between the two groups in life expectancy, quality adjusted life expectancy and costs were calculated, and an incremental cost-effectiveness ratio (difference in costs/difference in QALE) was calculated and compared with the current NICE position, where interventions with a cost-effectiveness ratio of less than £20,000 per QALY are considered good value for money. When calculating cost-effectiveness, all future costs and outcomes were discounted at an annual rate of 3.5% in line with current UK guidelines.

Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

Supplementary Data: Figure 1. Flow chart of total cohort selection from the full clinic registry and subgroup selection.



Abbreviations and definitions: Alcohol excess defined as an average intake of > 21 (male) or 14 (female) units per week for a prolonged period within 5 years prior to baseline visit; HH, hereditary haemochromotosis (HFE C282Y homozygous and C282Y/H63D compound heterozygous); AATD, alpha-1 antitrypsin deficiency (ZZ and SZ genotype); PBC/AIH, primary biliary cirrhosis-autoimmune hepatitis overlap syndrome; T2DM, type 2 diabetes mellitus; HbA_{1c}, glycated haemoglobin.

Moolla et al. A multi-disciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health – Supplementary Data

Supplementary Data: Figure 2. Net changes to medication prescriptions between baseline and follow-up in patients with T2DM at baseline