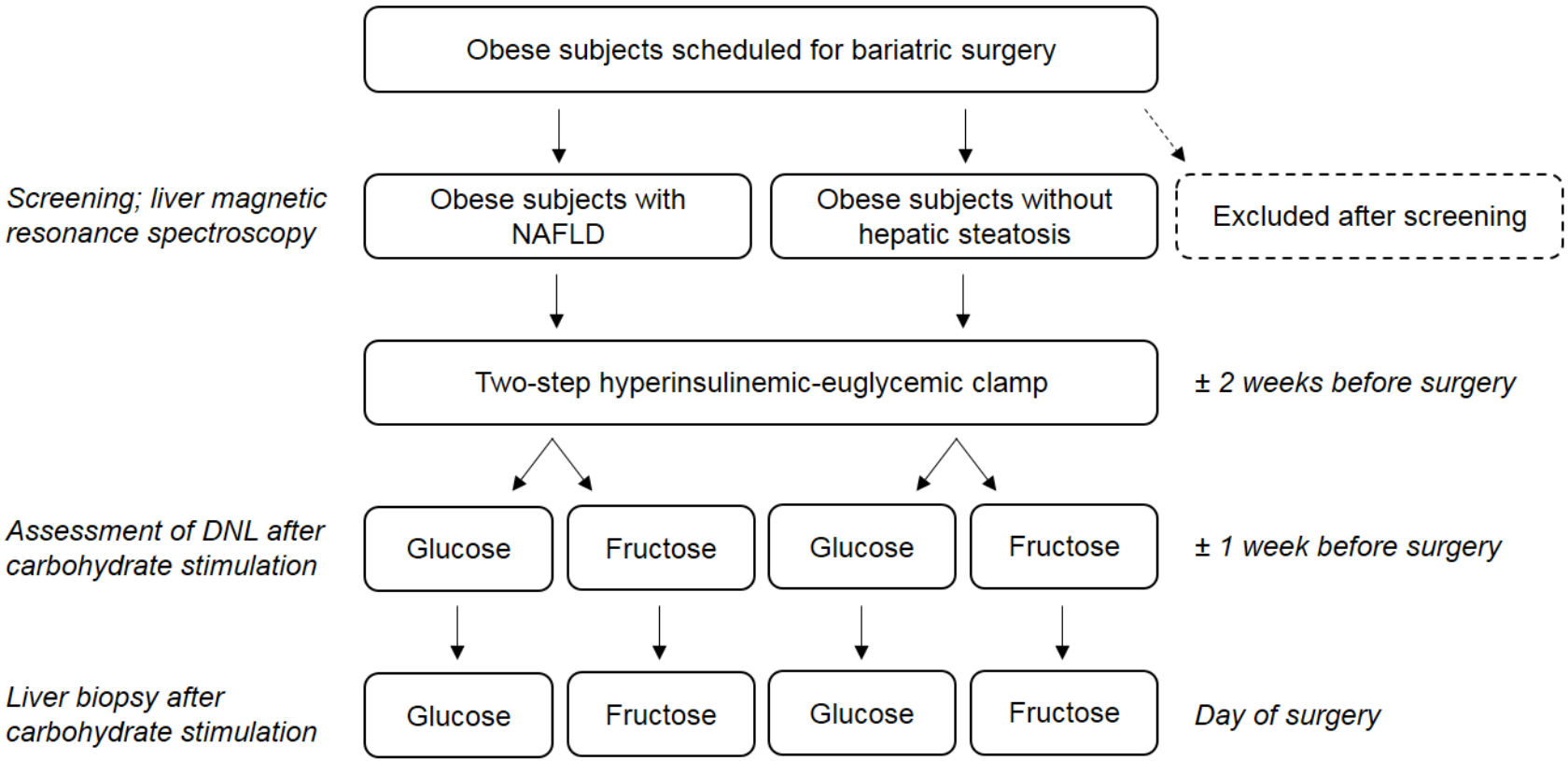


Supplementary Figure S1. Schematic of study design and main study procedures.

Supplementary Table S1. Baseline dietary intake.

	Controls			NAFLD		
	All (n=15)	Glucose (n=8)	Fructose (n=7)	All (n=16)	Glucose (n=8)	Fructose (n=8)
Energy from fat (%)	35±5	33±4	36±5	36±6	38±7	35±6
Energy from carbohydrate (%)	44±5	47±4	43±6	44±4	44±5	44±4
Energy from protein (%)	20±3	20±2	21±4	19±3	18±3	20±3
Energy from alcohol (%)	0 (0–1)	0 (0-2)	0 (0-1)	0 (0–0)	0 (0-0)	0 (0-2)

Data are mean±SD or median (IQR), depending on type and distribution. Baseline dietary intake did not differ among groups.

Supplementary Table S2. Data from two-step hyperinsulinemic-euglycemic clamp studies.

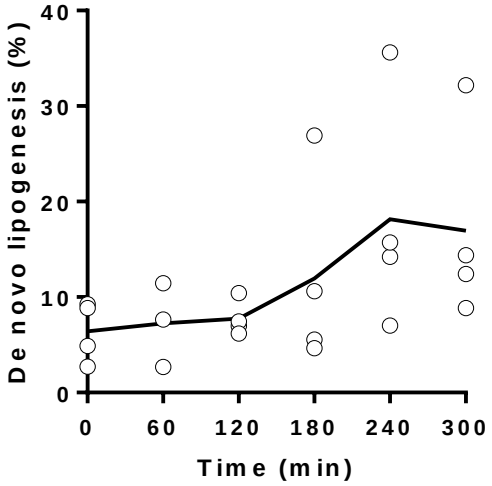
	Controls (n=15)	NAFLD (n=16)
During basal conditions (fasting)		
Glucose (mmol/l)	4.8±0.4	5.6±1.8
Insulin (pmol/l)	80±26	158±78[B]
Glucagon (ng/l)	86±18	93±23
Cortisol (nmol/l)	205±104	146±48
EGP (µmol·kg^{-1}·min^{-1})	7.7±0.6	8.3±1.7
NEFA (mmol/l)	0.66±0.19	0.65±0.18
Glucose oxidation (mg·kg^{-1}·min^{-1})	0.36 (0.26–0.71)	0.50 (0.15–1.04)
Fat oxidation (mg·kg^{-1}·min^{-1})	0.88±0.18	0.92±0.29
Resting energy expenditure (kcal·kg^{-1}·day^{-1})	14.8±1.7	15.7±1.5
During low-dose insulin infusion (step 1)		
Glucose (mmol/l)	5.2±0.5	5.4±1.0
Insulin (pmol/l)	286±63	351±72[A]
Glucagon (ng/l)	75±19	85±25
Cortisol (nmol/l)	232±95	231±79
EGP (µmol·kg^{-1}·min^{-1})	1.9±1.0	3.2±1.6[B]
Insulin suppression of EGP (%)	76±11	62±13[B]
NEFA (mmol/l)	0.07 (0.04–0.11)	0.14 (0.08–0.24)[B]
Insulin suppression of NEFA (%)	87±9	74±17[B]
Rd (µmol·kg^{-1}·min^{-1})	12.8 (11.1–14.7)	9.6 (8.6–11.5)[B]
Insulin stimulation of Rd (%)	168 (150–189)	121 (102–148)[B]
During high-dose insulin infusion (step 2)		
Glucose (mmol/l)	5.1±0.3	5.0±0.4
Insulin (pmol/l)	755±148	828±125
Glucagon (ng/l)	64±22	79±18
Cortisol (nmol/l)	203±79	190±88
EGP (µmol·kg^{-1}·min^{-1})	0.0 (0.0–0.3)	0.2 (0.0–1.7)
Insulin suppression of EGP (%)	100 (95–100)	98 (79–100)
NEFA (mmol/l)	0.01 (0.01–0.02)	0.03 (0.01–0.09)[A]
Insulin suppression of NEFA (%)	100 (97–100)	96 (90–100)[A]
Rd (µmol·kg^{-1}·min^{-1})	33.2±8.4	24.0±8.8[B]
Insulin stimulation of Rd (%)	441±131	302±125[B]

Data are mean±SD or median (IQR), depending on type and distribution. [A]$p<0.05$; [B]≤ 0.01 on t-test or Mann-Whitney U.

Supplementary Table S3. Characteristics of historic controls for fasting hepatic gene expression.

	Controls (n=8)	NAFLD (n=8)
Female	4 (50)	5 (62)
Age (years)	42±14	45±8
BMI (kg/m^2)	41±5	44±5
Glucose (mmol/l)	4.9±0.5	5.0±0.5
Insulin (pmol/l)	109±39	210±190
Triglycerides (mmol/l)	1.1 (0.8–1.6)	1.7 (0.7–2.9)
Alanine aminotransferase (U/l)	24±6	45±33
Insulin suppression of EGP (%)	77±12	70±13
Insulin suppression of FA (%)	83±11	73±15
Insulin stimulation of Rd (μmol·kg^{-1}·min^{-1})	34.5±12.8	21.9±10.2
Liver fat (%)	3.6 (1.5–4.5)	19.0 (11.4–24.4)[A]

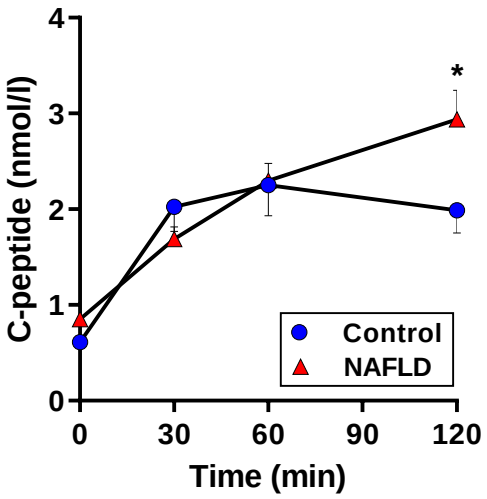
Data are count (%), mean±SD or median (IQR), depending on type and distribution. [A]$p<0.01$ on Mann-Whitney U.



Supplementary Figure S2. Pilot experiment assessing rates of DNL after carbohydrate ingestion. In all subjects, hepatic DNL was elevated at 240 min; in 3 subjects, it started to decrease at 300 min. Points are individual subjects (n=4).

Supplementary Table S4. Primer sequences of genes assessed by q-RT-PCR.

Gene	Forward	Reverse
ChREBPα (MLXIPL)	AGTGCTTGAGCCTGGCCTAC	TTGTTCAGGCGGATCTTGTC
ChREBPβ	AGCCGATTCCAGGTGAGG	TTGTTCAGGCGGATCTTGTC
RPLP0	TCGACAATGGCAGCATCTAC	ATCCGTCTCCACAGACAAGG



Supplementary Figure S3. Oral glucose ingestion stimulated C-peptide release in control and NAFLD subjects. In line with insulin excursions (**Figure 1F**), serum C-peptide concentrations started to decrease after 60min in control subjects, whereas they continued to increase up to 120min in NAFLD subjects (n=8 per group). Data are mean±SEM. *p<0.05 on t-test.