Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial

Ornella Verrastro, Simona Panunzi*, Lidia Castagneto-Gissey, Andrea De Gaetano, Erminia Lembo, Esmeralda Capristo, Caterina Guidone, Giulia Angelini, Francesco Pennestrì, Luca Sessa, Fabio Maria Vecchio, Laura Riccardi, Maria Assunta Zocco, Ivo Boskoski, James R Casella-Mariolo, Pierluigi Marini, Maurizio Pompili, Giovanni Casella, Enrico Fiori, Francesco Rubino, Stefan R Bornstein, Marco Raffaelli, Geltrude Mingrone*

Summary

Background Observational studies suggest that bariatric–metabolic surgery might greatly improve non-alcoholic steatohepatitis (NASH). However, the efficacy of surgery on NASH has not yet been compared with the effects of lifestyle interventions and medical therapy in a randomised trial.

Methods We did a multicentre, open-label, randomised trial at three major hospitals in Rome, Italy. We included participants aged 25–70 years with obesity (BMI 30–55 kg/m²), with or without type 2 diabetes, with histologically confirmed NASH. We randomly assigned (1:1:1) participants to lifestyle modification plus best medical care, Roux-en-Y gastric bypass, or sleeve gastrectomy. The primary endpoint of the study was histological resolution of NASH without worsening of fibrosis at 1-year follow-up. This study is registered at ClinicalTrials.gov, NCT03524365.

Findings Between April 15, 2019, and June 21, 2021, we biopsy screened 431 participants; of these, 103 (24%) did not have histological NASH and 40 (9%) declined to participate. We randomly assigned 288 (67%) participants with biopsy-proven NASH to lifestyle modification plus best medical care (n=96 [33%]), Roux-en-Y gastric bypass (n=96 [33%]), or sleeve gastrectomy (n=96 [33%]). In the intention-to-treat analysis, the percentage of participants who met the primary endpoint was significantly higher in the Roux-en-Y gastric bypass group (54 [56%]) and sleeve gastrectomy group (55 [57%]) compared with lifestyle modification (15 [16%]; p<0·0001). The calculated probability of NASH resolution was 3·60 times greater (95% CI 2·19–5·92; p<0·0001) in the Roux-en-Y gastric bypass group and 3·67 times greater (2·23–6·02; p<0·0001) in the sleeve gastrectomy group compared with in the lifestyle modification group. In the per protocol analysis (236 [82%] participants who completed the trial), the primary endpoint was met in 54 (70%) of 77 participants in the Roux-en-Y gastric bypass group and 55 (70%) of 79 participants in the sleeve gastrectomy group, compared with 15 (19%) of 80 in the lifestyle modification group (p<0·0001). No deaths or life-threatening complications were reported in this study. Severe adverse events occurred in ten (6%) participants who had bariatric-metabolic surgery, but these participants did not require re-operations and severe adverse events were resolved with medical or endoscopic management.

Interpretation Bariatric-metabolic surgery is more effective than lifestyle interventions and optimised medical therapy in the treatment of NASH.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease globally, affecting 55% of people with type 2 diabetes[1] and 75% of those with obesity.[2] Non-alcoholic steatohepatitis (NASH) is the progressive form of the disease and is characterised by liver cell injury (hepatocellular ballooning) and inflammation, which induce liver fibrosis.[3] NASH can lead to end-stage liver disease (cirrhosis, liver failure, and cancer) and is associated with increased risk of cardiovascular disease.[3] By 2030, NASH will affect 27 million people in the USA alone.[4]

Weight loss is generally recommended in people with NAFLD or NASH,[5] but no specific surgical or pharmacologic interventions are approved for these conditions. No drugs have yet received approval by the US Food and Drug Administration (FDA) or by the European Medicines Agency as a treatment for NASH or NAFLD.

Hepatic inflammation drives fibrosis, which is a main predictor of advancing disease and complications of NASH. Therefore, control of fibrosis and resolution of the inflammation that drives it are important therapeutic goals.[6] The FDA and other agencies recommend that

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*Joint first authors

Università Cattolica del Sacro Cuore, Rome, Italy (O Verrastro PhD, E Lembo MD, E Capristo MD, G Angelini PhD, L Riccardi MD, M A Zocco MD, I Boskoski MD, M Pompili MD, Prof M Raffaelli MD, Prof G Mingrone MD PhD); **CNR-IASI, Laboratorio di Biomatematica, Consiglio Nazionale delle Ricerche, Istituto di Analisi dei Sistemi ed Informatica, Rome, Italy** (S Panunzi PhD, A De Gaetano PhD); **Department of Surgical Sciences, Sapienza University of Rome, Rome, Italy** (L Castagneto-Gissey MD PhD, Prof E Fiori MD); **Department of Medical and Surgical Sciences** (E Capristo, C Guidone MD, F Pennestrì MD, L Sessa MD, L Riccardi, M A Zocco, I Boskoski, M Pompili, G Casella MD, Prof M Raffaelli, Prof G Mingrone), **Department of Pathology and Laboratory Medicine** (Prof F M Vecchio MD), **Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy; Department of Endocrine and Bariatric-Metabolic Surgery, San Camillo Hospital, Rome, Italy** (J R Casella-Mariolo MD, P Marini MD); **Bariatric and Bariatric-Metabolic Surgery** (Prof F Rubino MD), **Division of Diabetes & Nutritional Sciences, School of Cardiovascular and Metabolic Medicine & Sciences, King's College Hospital, London UK** (Prof S R Bornstein MD, Prof G Mingrone); **Department of Medicine III, Universitätsklinikum Carl Gustav Carus an de**

Technischen Universität Dresden, Dresden, Germany (Prof S R Bornstein)

Correspondence to: Prof Geltrude Mingrone, School of Cardiovascular and Metabolic Medicine & Sciences, King's College London, London, UK
geltrude.mingrone@kcl.ac.uk

Research in context

Evidence before this study

Non-alcoholic steatohepatitis (NASH) is a progressive form of liver disease that is characterised by liver cell injury (hepatocellular ballooning) and inflammation, in addition to steatosis, with consequent liver fibrosis. NASH can lead to end-stage liver disease, such as cirrhosis and cancer, and is associated with increased risk of cardiovascular disease and death. There are no approved therapeutic options for NASH and the treatment is largely limited to lifestyle modifications. We searched PubMed from inception to Feb 20, 2023, using the terms "bariatric surgery" "metabolic surgery" bariatric-metabolic surgery", "metabolic-bariatric surgery", and "non-alcoholic steatohepatitis", or "non-alcoholic fatty liver disease". We excluded non-English references. We searched for randomised trials and observational studies. We did not find randomised trials exploring the efficacy of bariatric-metabolic surgery on NASH. Literature data suggest that bariatric-metabolic surgery might be an ideal approach to treat NASH in people with obesity, with or without diabetes, owing to the surgery's ability to resolve NASH and at least halt or improve fibrosis in a substantial proportion of individuals. However, the efficacy of surgery on NASH has not yet been shown in a randomised trial and compared with the effects of lifestyle interventions and best medical care.

Added value of this study

To our knowledge, BRAVES is the first randomised trial comparing the effects of bariatric-metabolic surgery with lifestyle modification plus best medical care in people with histologically confirmed NASH. Surgical treatment resulted in NASH resolution with no worsening of fibrosis according to pathologist diagnostic assessment and on the non-alcoholic fatty liver disease activity score algorithm proposed by the NASH Clinical Research Network. The per protocol analysis showed that this goal was achieved in 70% of patients who had either Roux-en-Y gastric bypass or sleeve gastrectomy, which far exceeded the effects of any drug tested until now in randomised trials. Importantly, the more severe the NASH and liver fibrosis the higher the proportions of patients with NASH resolution. Improvement of at least one stage of fibrosis severity without worsening of NASH was almost twice that in the control group.

Implications of all the available evidence

In participants with a non-alcoholic fatty liver disease activity score of at least 4 and stages 2 or 3 fibrosis, the probability of NASH resolution without worsening of fibrosis was 4·40 times higher in the Roux-en-Y gastric bypass group and 3·43 times higher in the sleeve gastrectomy group than in the lifestyle modification group. In this subgroup, the improvement of at least one stage of fibrosis was almost double after both Roux-en-Y gastric bypass and sleeve gastrectomy than after lifestyle modification. The ability of surgery to control and even improve fibrosis associated with NASH is of particular clinical relevance given the fact that fibrosis is the main predictor of liver complications and cardiovascular mortality and morbidity in NASH. These findings further support the use of bariatric-metabolic surgery in people with metabolic diseases. NASH should be considered as an important factor in decision making around prioritisation of surgery in people with obesity and type 2 diabetes.

meaningful endpoints for clinical trials that are aimed at testing efficacy of interventions for NASH should include resolution of NASH as well as improvement of the severity of fibrosis.

Bodyweight loss of at least 10% is necessary to achieve clinically significant rates of NASH resolution.[5] However, such weight loss is rarely attainable with lifestyle interventions alone.[7] Novel anti-obesity medications, such as semaglutide or tirzepatide, can induce a 12–17% weight loss.[8,9] In a randomised trial semaglutide achieved resolution of NASH with no worsening of fibrosis in 59% of people versus 17% in the placebo group.[10] However, the study found no significant differences in fibrosis improvement between semaglutide and placebo.[10]

Bariatric-metabolic surgery can induce long-term weight reduction of up to 30%[11] and substantial amelioration or even long-term remission of type 2 diabetes.[12–17] In observational studies,[18,19] bariatric-metabolic surgery improved both NASH and fibrosis. Lassailly and colleagues[18] reported resolution of NASH in 54 (84%) of 64 liver samples from people with severe obesity at 5-year follow-up, with improved liver fibrosis in 57 (70%) participants.[18] Similar findings were also reported in another small observational study of 66 participants.[19]

These data suggest that bariatric-metabolic surgery might be an ideal approach to treat NASH in people with obesity, with or without diabetes, owing to the surgery's ability to resolve NASH and at least halt or improve fibrosis in a substantial proportion of individuals. However, the efficacy of surgery on NASH has not yet been confirmed in a randomised trial and compared with the effects of lifestyle interventions and medical therapy.

Here, we report the results of an open-label, multicentre, trial that was specifically designed to investigate and compare the efficacy and safety of bariatric-metabolic surgery with lifestyle intervention plus best medical care as a treatment of histologically confirmed NASH.

Methods

Study design and participants

BRAVES is a 52-week open-label, multicentre, randomised trial comparing lifestyle modification plus best medical care, Roux-en-Y gastric bypass, or sleeve gastrectomy for

the treatment of histologically confirmed NASH in people with obesity and with or without type 2 diabetes done in three major hospitals in Rome, Italy. The study was done in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The protocol was approved by the ethics committees of Fondazione Policlinico A Gemelli, Policlinico Umberto I, and Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy. Written informed consent was obtained at enrolment and again before surgical procedures.

We included participants with obesity (BMI 30–55 kg/m²), with or without type 2 diabetes, with histologically confirmed NASH (NAFLD activity score of at least 1 in each single item) and no evidence of another form of liver disease. Exclusion criteria are given in the appendix (p 2).

This study is registered at ClinicalTrials.gov, NCT03524365.

Diagnosis of NASH and staging of fibrosis

We assessed the likelihood of NASH and liver fibrosis using the NAFLD fibrosis score.[20] Specifically, eligibility for surgery included participants with type 2 diabetes and BMI of at least 30 kg/m² (or 27·5 kg/m² in participants of Asian descent) as per accepted worldwide guidelines.

An NAFLD fibrosis score greater than –1·455 confers high probability of fibrosis and NASH.[20] All participants with an NAFLD fibrosis score greater than –1·455 were therefore considered appropriate candidates for liver biopsy for histological confirmation of diagnosis. Histological diagnosis of NASH was established according to widely accepted criteria, using the NAFLD activity score algorithm proposed by the NASH Clinical Research Network (CRN).[3] These criteria include presence of steatosis in more than 5% of hepatocytes, hepatocellular ballooning, and lobular inflammatory infiltrates.[3]

We also assessed the presence and stages of fibrosis using the NASH-CRN system:[3] stage 0 indicates no fibrosis, stage 1 centrilobular pericellular fibrosis, stage 2 centrilobular and periportal fibrosis, stage 3 bridging fibrosis, and stage 4 cirrhosis.

At the end of the study, each biopsy was assessed centrally and sequentially by two independent expert hepatopathologists (FMV and JRC-M) to assess NAFLD activity score and fibrosis stage (according to NASH-CRN criteria). Each liver biopsy at 1-year follow-up was analysed together with the corresponding baseline biopsy.

The hepatopathologists were masked to the treatment, characteristics of the participants, and each other's assessments. The two pathologists agreed on the diagnosis of NASH in all cases. Overall, hepatopathologists agreed on NAFLD activity scores and fibrosis stages in 35% of the assessments. However, the agreement on the grades of individual NAFLD activity score components was 95% for ballooning, 82% for inflammation, and 60% for steatosis. The agreement on the presence and single stages of fibrosis was 69%.

In cases of discordant assessment on any variable, a consensus was reached by discussion or joint assessment of the two hepatopathologists. If a consensus was not reached, a third independent, qualified hepatopathologist could have made the final decision. However, each time the two hepatopathologists reached an agreement and the third hepatopathologist was never required.

Details of randomisation, interventions, screening, and demographic measurements are reported in the appendix (pp 2–6).

Ultrasound-guided percutaneous liver biopsy

Before performing ultrasound guided percutaneous liver biopsy using local anaesthesia, we measured complete blood count, including platelet count, and prothrombin time, and international normalised ratio. If the participants were in anticoagulation therapy, warfarin was discontinued at least 5 days before the scheduled procedure and substituted with low molecular heparin, which was discontinued at least 12 h before the biopsy. Antiplatelets (ie, aspirin, ticlodipine, clopidogrel, IIb/IIIa receptor, prothrombin receptor antagonists, and non-steroidal anti-inflammatory drugs) were discontinued at least 10 days before liver biopsy. Antiplatelet therapy was restarted 48–72 h after liver biopsy and warfarin was restarted the day following liver biopsy. Participants were monitored in hospital for the 48 h following the liver biopsy.

See Online for appendix

Adverse events

Severity, study intervention relationship, action taken, and outcomes of the adverse events were recorded in the electronic health records.

Biochemical analysis

We measured plasma glucose by the glucose oxidase method and insulin was assayed by microparticle enzyme immunoassay; we measured triglycerides, total cholesterol, and HDL cholesterol using an enzymatic colorimetric method (appendix p 6).

Outcomes

The primary endpoint of this study was the histological resolution of NASH without worsening of fibrosis, defined as an increase of one stage or more on the NASH-CRN fibrosis score[6] at 1-year follow-up. NASH resolution was defined as presence of a CRN inflammation score of 0 or 1 and no hepatocyte ballooning (score of 0). Worsening of liver fibrosis was defined as an increase of one stage or more on the Kleiner fibrosis classification scale.

The main secondary endpoint of the study was improvement in liver fibrosis by at least one stage of the NASH-CRN fibrosis score[3] with no worsening of NASH.[6] Worsening of NAFLD activity score was defined as an increase of at least 1 point in either the lobular inflammation score or the hepatocyte ballooning score, according to the NASH-CRN criteria, at 1-year follow-up.

	Lifestyle modification (n=96)	Roux-en-Y gastric bypass (n=96)	Sleeve gastrectomy (n=96)	Surgical Interventions (n=192)
Age, years	47·81 (10·24)	47·23 (8·30)	47·21 (8·97)	47·22 (8·62)
Bodyweight, kg	118·49 (22·25)	125·76 (20·07)	119·21 (19·17)	122·49 (19·85)
BMI, kg/m²	41·87 (6·30)	42·86 (4·62)	41·38 (4·32)	42·12 (4·52)
NAFLD activity score	4·17 (0·97)	4·14 (0·97)	4·16 (1·07)	4·15 (1·02)
HbA_{1c}, %	6·32% (1·83)	6·84% (2·36)	5·93% (1·37)	6·40% (1·99)
Glucose, mmol/L	6·37 (2·26)	6·66 (3·24)	5·81 (1·36)	6·22 (2·48)
Insulin, U/L	24·92 (14·31)	26·79 (12·22)	29·04 (19·17)	27·87 (15·93)
HOMA-IR	6·91 (3·99)	8·41 (6·29)	7·89 (6·81)	8·16 (6·53)
HDL cholesterol, mmol/L	1·12 (0·34)	1·18 (0·42)	1·15 (0·40)	1·16 (0·41)
LDL cholesterol, mmol/L	2·96 (0·81)	3·17 (1·19)	3·11 (1·00)	3·14 (1·10)
Total cholesterol, mmol/L	4·89 (0·97)	5·15 (1·14)	5·09 (1·15)	5·12 (1·14)
Triglycerides, mmol/L	1·81 (0·91)	1·82 (0·83)	1·77 (0·83)	1·79 (0·83)
Aspartate aminotransferase, U/L	33·48 (19·93)	35·04 (23·03)	28·52 (13·32)	31·84 (19·12)
Alanine aminotransferase, U/L	37·95 (19·79)	45·99 (36·44)	40·20 (25·79)	43·14 (31·70)

Data are mean (SD). HOMA-IR=homoeostasis model assessment-estimated insulin resistance. NAFLD=non-alcoholic fatty liver disease.

Table 1: **Baseline characteristics (intention-to-treat population)**

Other pre-specified secondary endpoints were safety, NAFLD activity score improvement of at least one stage, worsening of fibrosis, diabetes control, insulin sensitivity, and lipid profile.

We did a post-hoc analysis to assess the primary endpoint as well as the main secondary endpoint of the study in participants with an NAFLD activity score of 4 or NAFLD activity score of at least 5 in the intention-to-treat (ITT) analysis and an NAFLD activity score of at least 4 and F2–F3 stage in the per protocol analysis.

Moreover, we computed the proportion of participants who had an improvement of at least 2 points in fibrosis stage in the three groups.

Statistical analysis

The sample size calculation was based on a large sample test for proportions using the approach of a pairwise comparison. In the present study three comparisons were planned: Roux-en-Y gastric bypass versus sleeve gastrectomy, Roux-en-Y gastric bypass versus lifestyle modification, and sleeve gastrectomy versus lifestyle modification.

We used adjustment of the nominal type I error to guarantee a control of the overall type I error, which was set to 0·05 (with κ the κth comparison and τ the total number of comparisons). The power was set to 80% and all the tests were two tailed. The first pairwise comparison (Roux-en-Y gastric bypass *vs* sleeve gastrectomy) was conducted under the hypothesis of rates of 80% NASH resolution in the Roux-en-Y gastric bypass group[18] and 55% in the sleeve gastrectomy group. The sample size for the comparison between Roux-en-Y gastric bypass and lifestyle modification was computed to detect a difference of 50% in the rate of NASH resolution: 80% in Roux-en-Y gastric bypass versus 30% in lifestyle modification, based on the assumption that the lifestyle modification would achieve resolution rates at best similar to those of liraglutide.[21] Hence, for the third comparison (sleeve gastrectomy *vs* lifestyle modification) we assumed a difference of 25 percentage points.

Under these assumptions, we calculated a sample size of 77 participants per group (with the maximum sample size derived from the third comparison). Considering an attrition rate of 20%, we enrolled 96 participants in each group for a total of 288 participants.

Analysis of the primary endpoint was done by both ITT and per protocol methods. All further analyses were done per protocol only. Following a conservative approach for ITT, all cases with no available data for the 1-year post-intervention biopsy were considered as failure of the treatment in the resolution of NASH. Thus, for the participants who dropped out of the study, the outcome was imputed as non-response.

We compared primary and secondary endpoints among the three intervention groups. For counts, we used a χ^2 test to study the association between variables of interest and groups. For NASH resolution and fibrosis improvement without NASH worsening, we computed relative risks (RRs) along with their 95% CIs, with lifestyle modification as reference treatment by the unconditional maximum likelihood estimation method (Wald method). We computed percent deltas of quantitative variables as $(X_{1year}-X_{bas})/X_{basr}\times100$, where X_{1year} represents the variable at 1 year after intervention and X_{bas} is the variable at baseline and assessed by ANOVA. We used a *t* test for independent samples to test possible differences of the variables of interest between responders (individuals with resolution of NASH without worsening of fibrosis) and non-responders.

We used univariable and multivariable generalised regression models with logarithm as link function (Zou's modified Poisson regression) to study the baseline determinants of the primary endpoint. Only predictors significant at a p value of 0·10 or less entered the multivariable model.

For each statistical test the type I error was set at 5% and the tests were two sided. We did multiple pairwise comparisons between each pair of interventions by adjusting for Bonferroni correction; post-hoc ANOVA tests were corrected using Tukey's honestly significant difference.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 15, 2019, and June 21, 2021, we screened 431 participants; of these, 103 (24%) were not eligible because of the absence of NASH and 40 (9%) declined to

	Lifestyle modification (n=80)	Roux-en-Y gastric bypass (n=77)	Sleeve gastrectomy (n=79)	Overall p value	Roux-en-Y gastric bypass *vs* lifestyle modification p value	Sleeve gastrectomy *vs* lifestyle modification p value	Sleeve gastrectomy *vs* Roux-en-Y gastric bypass p value
Age, years	47·95 (10·39)	46·44 (8·50)	46·84 (8·81)	0·57	0·57	0·73	0·96
Bodyweight, kg							
Baseline	116·07 (22·9)	127·69 (19·54)	118·84 (18·68)	0·0013	0·0013	0·67	0·020
1 year	109·82 (24·15)	87·02 (15·66)	89·77 (16·45)	..	..	..	..
Change, %	–5·48% (7·57)	–31·80% (7·50)	–23·98% (11·58)	<0·0001	<0·0001	<0·0001	<0·0001
BMI, kg/m²							
Baseline	41·16 (6·4)	43·39 (4·14)	40·76 (3·74)	0·0018	0·013	0·87	0·0028
1 year	39·07 (7·55)	29·70 (4·26)	30·82 (4·08)	..	..	..	..
Change, %	–5·38% (7·61)	–31·50% (7·92	–23·91% (11·53)	<0·0001	<0·0001	<0·0001	<0·0001
NAFLD activity score							
Baseline	4·21 (1·00)	4·21 (1·00)	4·18 (1·11)	0·97	1	0·98	0·98
1 year	3·45 (1·31)	1·82 (0·82)	1·99 (1·12)	..	..	..	..
Change, %	–17·08% (28·59)	–56·20% (19·57)	–52·83% (25·46)	<0·0001	<0·0001	<0·0001	0·67
Fibrosis stage							
F0							
Baseline	0	1 (1·3%)	1 (1·3%)	0·60	0·98	0·99	1
1 year	2 (2·5%)	7 (9·1%)	9 (11·4%)	0·090	0·15	0·058	0·83
F1							
Baseline	34 (42·5%)	38 (49·3%)	41 (51·9%)	0·47	0·48	0·30	0·87
1 year	41 (51·2%)	58 (75·3%)	54 (68·3%)	0·0049	0·0031	0·044	0·43
F2							
Baseline	31 (38·8)	33 (42·8%)	28 (35·4%)	0·63	0·72	0·78	0·43
1 year	26 (32·5%)	11 (14·3%)	12 (15·2%)	0·0062	0·012	0·018	1
F3							
Baseline	15 (18·8%)	5 (6·5%)	9 (11·4%)	0·062	0·039	0·28	0·43
1 year	11 (13·8%)	1 (1·3%)	3 (3·8%)	0·0031	0·0084	0·053	0·63
HbA_{1c}, %							
Baseline	6·42% (1·87)	6·93% (2·23)	6·00% (1·21)	0·0091	0·23	0·38	0·0063
1 year	5·87% (1·87)	5·95% (1·74)	5·55% (0·60)	..	..	..	..
Change, %	–1·49% (57·16)	–10·66% (25·18)	–3·46% (28·29)	0·18	0·16	0·74	0·50
Glucose, mmol/L							
Baseline	6·72 (2·41)	6·90 (3·57)	5·72 (1·36)	0·012	0·91	0·058	0·016
1 year	5·75 (2·28)	4·39 (0·57)	4·56 (0·86)	..	..	..	..
Change, %	–10·22% (26·11)	–27·19% (20·62)	–18·11% (16·09)	<0·0001	<0·0001	0·068	0·025
Insulin, U/L							
Baseline	21·76 (7·59)	28·96 (11·24)	31·75 (19·58)	0·0020	0·026	0·0017	0·54
1 year	17·77 (8·33)	8·01 (4·02)	14·99 (16·85)	..	..	..	..
Change, %	–11·69% (47·57)	–52·19% (131·60)	–49·48% (43·72)	0·050	0·061	0·10	0·99
Homa-IR							
Baseline	6·64 (3·14)	9·40 (6·56)	8·63 (7·33)	0·076	0·065	0·26	0·79
1 year	4·63 (2·73)	1·57 (0·90)	3·54 (5·29)	..	..	..	..
Change, %	–19·97% (49·47)	–62·01% (119·84)	–57·06% (40·35)	0·029	0·032	0·080	0·95
HDL cholesterol, mmol/L							
Baseline	1·14 (0·38)	1·13 (0·36)	1·09 (0·25)	0·62	0·98	0·63	0·74
1 year	1·19 (0·35)	1·37 (0·30)	1·28 (0·33)	..	..	..	..
Change, %	7·25% (25·55)	29·92% (43·55)	18·53% (24·10)	0·0005	0·0003	0·11	0·081
LDL cholesterol, mmol/L							
Baseline	2·97 (0·77)	3·23 (1·23)	3·11 (1·00)	0·39	0·35	0·74	0·76
1 year	2·66 (0·91)	2·21 (0·80)	2·84 (0·85)	..	..	..	..
Change, %	–7·34% (30·69)	–24·60% (34·75)	–5·87% (21·01)	0·0002	0·0028	0·96	0·0003

(Table 2 continues on next page)

	Lifestyle modification (n=80)	Roux-en-Y gastric bypass (n=77)	Sleeve gastrectomy (n=79)	Overall p value	Roux-en-Y gastric bypass *vs* lifestyle modification p value	Sleeve gastrectomy *vs* lifestyle modification p value	Sleeve gastrectomy *vs* Roux-en-Y gastric bypass p value
(Continued from previous page)							
Total cholesterol, mmol/L							
Baseline	4·92 (0·97)	5·16 (1·21)	5·01 (1·13)	0·45	0·44	0·90	0·68
1 year	4·52 (1·08)	4·10 (0·90)	4·71 (0·97)	..	..	..	..
Change, %	–6·58% (21·68)	–18·08% (21·65)	–4·59% (13·86)	<0·0001	0·0015	0·81	<0·0001
Triglycerides, mmol/L							
Baseline	1·72 (0·94)	1·81 (0·78)	1·76 (0·81)	0·83	0·82	0·95	0·95
1 year	1·48 (0·83)	1·11 (0·49)	1·31 (0·60)	..	..	..	..
Change, %	–7·26% (40·04)	–33·05% (28·82)	–18·99% (45·29)	0·0006	0·0004	0·17	0·067
Aspartate aminotransferase, U/L							
Baseline	35·29 (21·41)	36·89 (24·20)	29·27 (14·05)	0·062	0·89	0·21	0·062
1 year	32·80 (17·65)	22·82 (8·69)	20·67 (8·58)	..	..	..	..
Change, %	7·75% (67·83)	–22·04% (39·73)	–23·60% (21·14)	0·0001	0·0006	0·0003	0·98
Alanine aminotransferase, U/L							
Baseline	38·34 (18·6)	48·09 (37·21)	41·78 (27·58)	0·13	0·12	0·76	0·39
1 year	33·65 (16·1)	22·86 (11·30)	22·63 (16·44)	..	..	..	..
Change, %	–0·22% (61·79)	–37·41% (37·52)	–38·70% (29·06)	<0·0001	<0·0001	<0·0001	0·98

Data are mean (SD) or n (%), unless otherwise indicated. p value from ANOVA (overall) and post-hoc pairwise comparisons (Roux-en-Y gastric bypass *vs* lifestyle modification, sleeve gastrectomy *vs* lifestlye modification, and sleeve gastrectomy *vs* Roux-en-Y gastric bypass) from Tukey's honestly significant difference test. HOMA-IR=homeostasis model assessment-estimated insulin resistance. NAFLD=non-alcoholic fatty liver disease.

Table 2: **Quantitative variables at baseline and at 1 year after intervention in the per protocol analysis**

participate. Therefore, 288 (67%) participants, all of them White, were deemed eligible for the study and were randomly assigned to lifestyle modification (n=96 [33%]) or Roux-en-Y gastric bypass (n=96 [33%]), or sleeve gastrectomy treatment (n=96 [33%]). 236 participants (82%) completed the trial (appendix p 6).

In the ITT population, participants in the three intervention groups did not differ in terms of sex, NAFLD activity score, fibrosis score, and prevalence of type 2 diabetes (table 1; appendix p 8). Type 2 diabetes was present in 35 (37%) people in the lifestyle modification group, 32 (33%) in the Roux-en-Y gastric bypass group, and 25 (26%) in the sleeve gastrectomy group (appendix p 8). However, the degree of diabetes control was different among groups (HbA_{1c} 7·87% [1·96] in the lifestyle modification group, 9·05% [3·01] in the Roux-en-Y gastric bypass group, and 7·06 [1·87%] in the sleeve gastrectomy group). There was a clinically small difference in baseline bodyweight and BMI, which tended to be higher in the Roux-en-Y gastric bypass group than in the other groups.

139 participants (48%) had stage F1 fibrosis, 114 (40%) had stage F2, 32 (11%) had stage F3, and three participants (1%) had stage F0 fibrosis; the mean NAFLD activity score grade was 4·19 (SD 1·03; table 2).

Among participants who completed the trial per protocol, 80 people underwent lifestyle modification, 77 had Roux-en-Y gastric bypass, and 79 had sleeve gastrectomy (table 2). 104 (44%) participants in the study were women, 132 (56%) were men, and the mean age was 47 years (SD 9·3; table 2; appendix p 9). We found no differences in age, sex, NAFLD activity score, or liver fibrosis at liver biopsy or liver function tests at baseline across the three groups (table 2; appendix p 9). We found a clinically small but statistically significant difference in baseline bodyweight, BMI, and HbA_{1c} levels, which were higher in the Roux-en-Y gastric bypass group (table 2). 34 (42%) participants in the lifestyle modification group, 25 (33%) in the Roux-en-Y gastric bypass group, and 17 (22%) in the sleeve gastrectomy group had type 2 diabetes at baseline (p=0·020; appendix p 9), but we found no significant difference between lifestyle modification and Roux-en-Y gastric bypass groups (p=0·60).

The anti-diabetic medications used in the three groups at baseline and at 1-year post-intervention are reported in the appendix (p 18).

In the per protocol set at baseline, the mean activity score for NASH was 4·2 (SD 1·0); 113 (48%) participants had stage F1 fibrosis and 121 (51%) had stages F2 and F3 fibrosis.

In the lifestyle modification group, 45 (56%) participants had weight loss of up to 5%, 13 (16%) had weight loss of 5–10%, 12 (15%) had weight loss of 11–15%, and 10 (12%) had weight loss greater than 15%. In the ITT analysis, the percentage of participants who met the primary endpoint (NASH resolution without worsening of fibrosis) was significantly higher after both Roux-en-Y gastric bypass (54 [56%] of 96) and sleeve gastrectomy (55 [57%] of 96) compared with lifestyle modification (15 [16%] of 96; p<0·0001; figure 1). The calculated probability of NASH

resolution was 3·60 times higher (95% CI 2·19–5·92; p<0·0001) for participants in the Roux-en-Y gastric bypass group and 3·67 times higher (2·23–6·02; p<0·0001) for participants in the sleeve gastrectomy group compared with in the lifestyle modification group (figure 2).

Stratifying by sex, women had a higher probability of reaching the primary endpoint after bariatric-metabolic surgery compared with men (2·93 [95% CI 1·57–5.45 in men *vs* 3·15 [1·44–6·90] in women after Roux-en-Y gastric bypass, and 2·66 [1·42–5·00 in men *vs* 3·64 [1·68–7·89] in women after sleeve gastrectomy; figure 2). The probability of reaching the primary endpoint increased for individuals without type 2 diabetes after Roux-en-Y gastric bypass (RR 3·49 [1·86–6·52]) and sleeve gastrectomy (3·88 [2·09–7·19]; figure 2).

NASH severity at baseline was associated with the probability of NASH resolution. The risk of resolution for participants in the Roux-en-Y gastric bypass and sleeve gastrectomy groups, compared with in the lifestyle modification group, increased with the increase of NASH severity, with the highest RR in individuals with an NAFLD activity score of 4 (figure 2).

Findings from the per protocol analysis are reported in the table and the appendix (p 9). In the per protocol analysis, 54 (70%) of 77 participants who had Roux-en-Y gastric bypass and 55 (70%) of 79 who had sleeve gastrectomy reached the primary endpoint, versus 15 (19%) of 80 in the lifestyle modification group (p<0·0001; appendix p 11). The probability of NASH resolution was 3·74 times higher (2·32–6·04; p<0·0001) in the Roux-en-Y gastric bypass group and 3·71 times higher (2·30–5·99; p<0·0001) in the sleeve gastrectomy group compared with in the lifestyle modification group (figure 3).

In the ITT population, the secondary endpoint of improvement of fibrosis of at least one stage without worsening of NASH was observed in 22 (23%) of 96 participants in the lifestyle modification group, 35 (37%) of 95 in the Roux-en-Y gastric bypass group, and 37 (39%) of 94 in the sleeve gastrectomy group (p=0·034; figure 1B). We also found a clinically and statistically significant reduction in liver enzyme concentrations after both surgical operations, whereas changes in liver enzymes were minor and not statistically significant after lifestyle modification (figure 1C, D).

In the per protocol analysis, improvement of fibrosis of at least one stage without worsening of NASH was observed in 22 (28%) of 80 participants in the lifestyle modification group, 35 (46%) of 76 in the Roux-en-Y gastric bypass group, and 37 (47%) of 78 in the sleeve gastrectomy group (p=0·017; appendix p 11). Only two (3%) individuals had regression to stage 0 fibrosis in the lifestyle modification group at 1 year after intervention, versus seven (9%) in the Roux-en-Y gastric bypass group and nine (12%) in the sleeve gastrectomy group.

Worsening of fibrosis occurred in 13 (16%) of 80 participants in the lifestyle modification group, six (8%) of 77 in the Roux-en-Y gastric bypass group, and six (8%) of 79 in the lifestyle modification group (p=0·13), independently of the initial severity, and the RRs for the two bariatric procedures relative to lifestyle modification were not significantly different from 1 (figure 3).

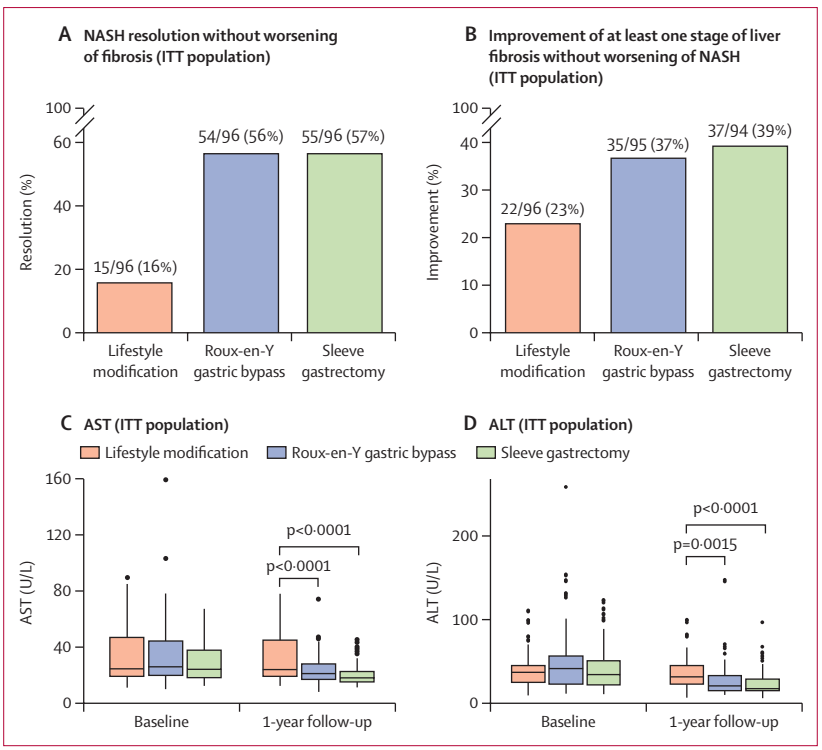

Figure 1: **Primary endpoint, secondary endpoint, AST, and ALT results in the ITT population**
(A) Percentage of patients with NASH resolution without worsening of fibrosis after lifestyle modification and best medical care, Roux-en-Y gastric bypass, and sleeve gastrectomy in the ITT population. Data at the top of the bars are the number of responders out of the total number of individuals and the percentage of responders in each intervention group. (B) Percentage of patients with improvement in liver fibrosis by at least one stage without worsening of NASH in the lifestyle modification, Roux-en-Y gastric bypass, and sleeve gastrectomy groups in the ITT population. Data at the top of the bars are the number of responders out of the total number of individuals and the percentage of responders in each intervention group. (C) AST concentrations at baseline and at 1-year follow-up in the lifestyle modification, Roux-en-Y gastric bypass, and sleeve gastrectomy groups in the ITT population. (D) ALT concentrations at baseline and at 1-year follow-up in the lifestyle modification, Roux-en-Y gastric bypass, and sleeve gastrectomy groups for the ITT population. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ITT=intention to treat. NASH=non-alcoholic steatohepatitis.

Improvement of at least one point in NAFLD activity score at 1-year follow-up occurred in 41 (51%) of 80 participants in the lifestyle modification group, in 75 (97%) of 77 in the Roux-en-Y gastric bypass group, and in 77 (97%) of 79 in the sleeve gastrectomy group; the probability of improvement was 1·9 [95% CI 1·53–2·36] in the Roux-en-Y gastric bypass and sleeve gastrectomy groups versus the lifestyle modification group (p<0·0001; figure 3).

We found a clinically and statistically significant reduction in liver-enzyme concentrations after both surgical operations, whereas changes in liver enzymes were minor and not statistically significant after lifestyle modification (table 2; appendix p 11).

Diabetes remission (defined as HbA_{1c}<6·5% without ongoing diabetes medications[22]) occurred in two (6%) of

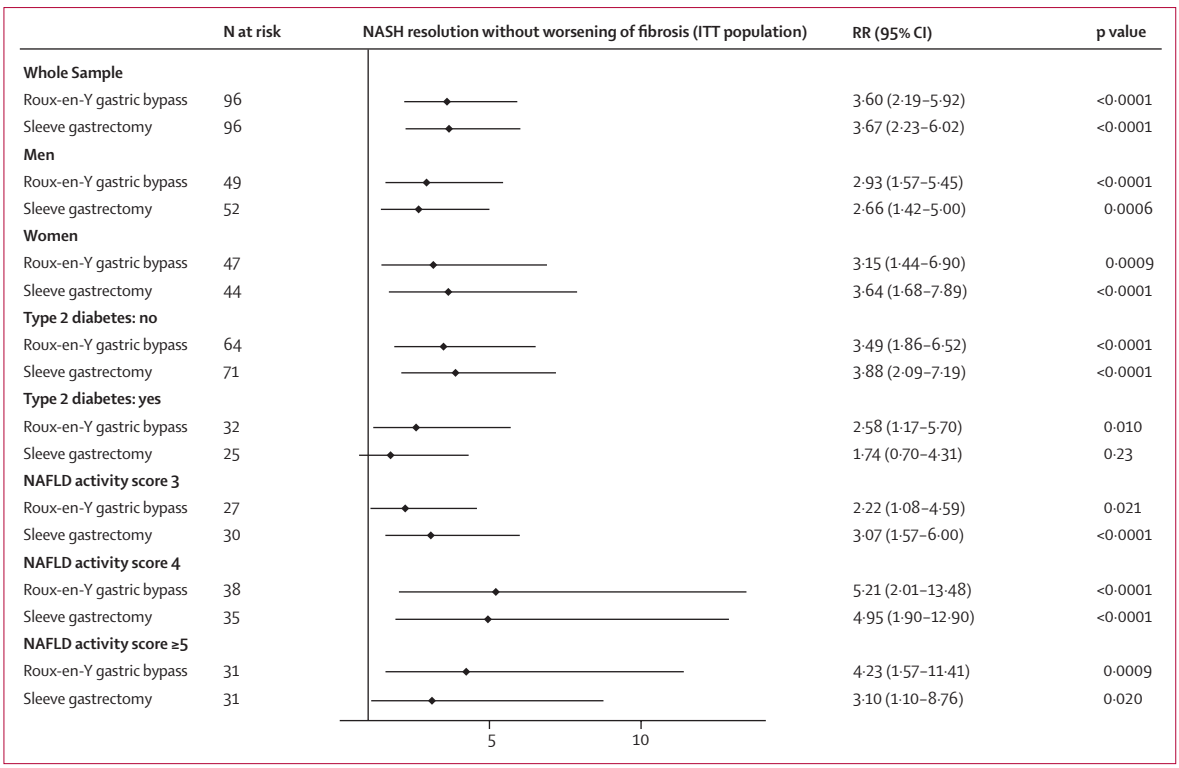

Figure 2: **Response for primary histological endpoint at 1-year follow-up and subgroup analysis stratified by sex, diabetes, and NASH grade in the ITT population**

N at risk, RRs, 95% CIs, and p values were calculated with unconditional maximum likelihood estimation (Wald). All RRs are unadjusted for potential baseline predictors. ITT=intention to treat. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. RR=risk ratio.

34 participants in the lifestyle modification group, 17 (68%) of 25 in the Roux-en-Y gastric bypass group, and 11 (65%) of 17 in the sleeve gastrectomy group (p<0·0001).

Participants in the Roux-en-Y gastric bypass group had greater improvements in plasma concentrations of triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol compared with those in the lifestyle modification and sleeve gastrectomy groups (p<0·05 for all comparisons; table 2). Similarly, participants in the Roux-en-Y gastric bypass group had greater reductions in fasting plasma glucose (from 6·9 mmol/L [SD 3·57] to 4·39 mmol/L [0·57]; –27·19% [20·62]), compared with those in the lifestyle modification group (from 6·72 mmol/L [2·41] to 5·75 mmol/L [2·28]; –10·22% [26·11]; p<0·0001) and sleeve gastrectomy group (from 5·72 mmol/L [1·36] to 4·56 mmol/L [0·86]; –18·11% [16·09]; p=0·025; table 2). We found a greater improvement in insulin resistance in participants in the Roux-en-Y gastric bypass group compared with in the other groups (homeostasis model assessment-estimated insulin resistance (–19·97% [49·47] in the lifestyle modification group, –62·01% [119·84] in the Roux-en-Y gastric bypass group, and –57·06% [40·35] in the sleeve gastrectomy group; p=0·029; table 2).

At baseline, 99 participants had an NAFLD activity score of at least 4 and stage 2 or 3 fibrosis: 37 (37%) participants in the lifestyle modification group, 35 (35%) in the Roux-en-Y gastric bypass group, and 27 (27%) in the sleeve gastrectomy group. Resolution of NASH without fibrosis worsening occurred in six (16%) participants in the lifestyle modification group, 25 (71%) in the Roux-en-Y gastric bypass group, and 15 (56%) in the sleeve gastrectomy group (p<0·0001; appendix p 13), with a probability of NASH resolution of 4·40 times higher (95% CI 2·06–9·43; p<0·0001) for Roux-en-Y gastric bypass and 3·42 times higher (1·53–7·67; p=0·0009) for sleeve gastrectomy compared with lifestyle modification (figure 3B).

In participants with an NAFLD activity score of at least 4 and stage 2 or 3 fibrosis, improvement of fibrosis of at least one stage was significantly different between interventions (15 [41%] of 37 in the lifestyle modification group, 28 [80%] of 35 in the Roux-en-Y gastric bypass group, and 19 [70%] of 27 in the sleeve gastrectomy group (p<0·0001; appendix p 13). Independently from NAFLD activity score, only 12 participants had an improvement of two stages of fibrosis: three (7%) of 46 in the lifestyle modification group, six (16%) of 38 in the Roux-en-Y gastric bypass group, and three (8%) of 37 in the sleeve gastrectomy group; p=0·33).

From the univariable generalised regression models, the probability of NASH resolution without worsening of

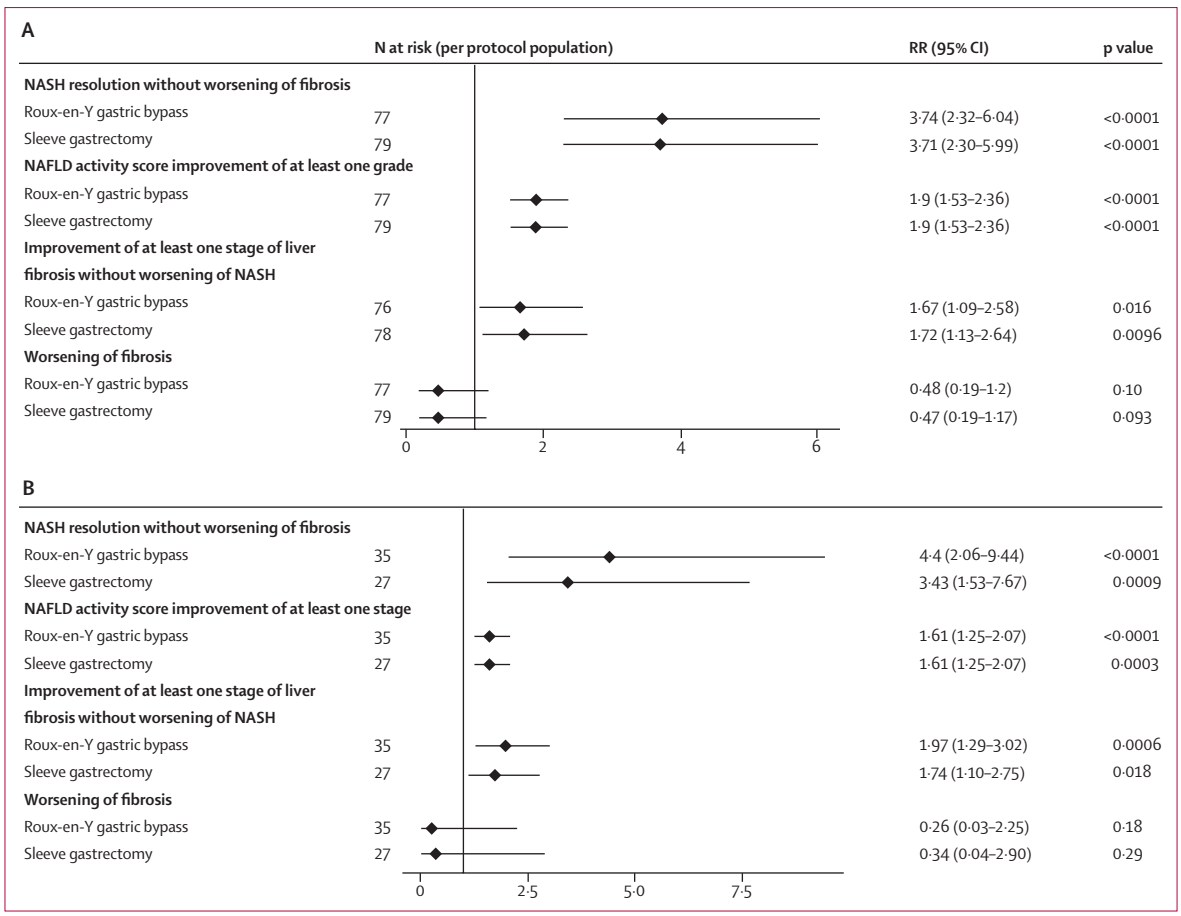

Figure 3: **Response for primary and secondary histological endpoints at 1-year follow-up for the per protocol population in the whole sample and in the sample with NAFLD activity score ≥4 and fibrosis stages F2 or F3**

(A) Response for primary and secondary histological endpoints at 1-year follow-up in the per protocol population. (B) Response for primary and secondary histological endpoints at 1-year follow-up in the subgroup of patients with severe NASH (NAFLD activity score ≥4 and stages 2, F2, or 3, F3, fibrosis) in the per protocol population. N at risk, RRs, 95% CIs, and p values were calculated with unconditional maximum likelihood estimation (Wald). All RRs are unadjusted for potential baseline predictors. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. RR=risk ratio.

fibrosis was higher for participants with lower concentrations of aspartate aminotransferase (AST; p=0·053) and HbA_{1c} (p=0·028) at baseline. A multivariable model that was adjusted for significant baseline predictors (AST and HbA_{1c}) found an adjusted RR for Roux-en-Y gastric bypass of 4·09 (95% CI 2·25–8·05) and sleeve gastrectomy of 3·56 (1·97–6·99).

The percentage of individuals who met the primary endpoint was computed for different classes of percentage weight loss (appendix p 19). The percentage of participants with NASH resolution without fibrosis worsening increased almost linearly with the degree of weight loss up to 20% weight reduction, then the increase was non-linear indicating a relatively smaller influence of weight loss on NASH resolution rate above a 20% weight-reduction threshold (appendix p 19).

Responders (participants who reached the primary endpoint) lost more weight, had higher rates of diabetes remission (p<0·0001), and had greater improvement of glycaemic control, insulin resistance, and transaminase concentrations compared with non-responders (appendix pp 14, 16).

There were no deaths or life-threatening complications in this study. Most adverse events were mild or moderate in severity and occurred mainly in the surgical groups (table 3). Severe adverse events occurred in ten (6%) of 156 participants who had bariatric-metabolic surgery. Surgical complications, however, did not require re-operations and were resolved with medical or endoscopic management. Complications due to ultrasound-guided liver biopsy were similar across the three groups (table 3).

Discussion

This study showed that bariatric-metabolic surgery was more effective than lifestyle intervention and best medical care as a treatment of NASH in people with obesity, with or without type 2 diabetes. Roux-en-Y gastric bypass and sleeve gastrectomy had similar efficacy on NASH, even though Roux-en-Y gastric bypass was generally more

	Roux-en-Y gastric bypass (n= 77)	Sleeve gastrectomy (n=79)	Lifestyle modification (n=80)
Early surgical adverse events			
Intestinal obstruction (functional stenosis of the entero-enteric anastomosis) and peritoneal abscess	1 (<1%)	0	0
Intussusception	2 (1%)	0	0
Incisional hernia	0	1 (<1%)	0
Internal hernia	1 (<1%)	0	0
Staple line leak	0	2 (1%)	0
Gastric stenosis (endoscopic balloon dilation)	0	2 (1%)	0
Haemoperitoneum	0	1 (<1%)	0
Late medical adverse events	0	0	0
Dumping syndrome	4 (2%)	1 (<1%)	0
Constipation	4 (2%)	6 (4%)	3 (2%)
Diarrhoea	2 (1%)	1 (<1%)	2 (1%)
Gastro-oesophageal reflux disease	2 (1%)	32 (19%)	4 (2%)
Kidney stones (need for nephrostomy)	1 (<1%)	0	1 (<1%)
Vomiting	2 (1%)	8 (5%)	3 (2%)
Anaemia	2 (1%)	0	0
Fatigue	2 (1%)	2 (1%)	3 (2%)
Biliary sludge	5 (3%)	4 (2%)	2 (1%)
Nausea	0	4 (2%)	4 (2%)
Epigastric pain	4 (2%)	1 (<1%)	2 (1%)
SARS-CoV-2 infection	5 (3%)	3 (2%)	6 (4%)
Alcoholism arising 10–12 months after intervention	1 (<1%)	0	0
Liver biopsy-related adverse events	0	0	0
Pain (right side or shoulder)	9 (5%)	10 (6%)	10 (6%)
Intraparenchymal bleeding	0	1 (<1%)	1 (<1%)
Extracapsular haematoma	1 (<1%)	0	0
Pain associated with fever	0	0	1 (<1%)

Data are n (%). Severe adverse events were four (5%) in the Roux-en-Y gastric bypass group, six (8%) in the sleeve gastrectomy group, and 0 in the lifestyle modification group. For the other adverse events, more than one adverse event occurred in the same patient. 169 adverse events occurred during the treatment period: 48 (28%) in the Roux-en-Y gastric bypass group, 79 (47%) in the sleeve gastrectomy group, and 42 (25%) in the lifestyle modification.

Table 3: **Adverse events**

effective at improving glycaemic control, lipid profile, insulin resistance, and weight loss. This finding might be explained by the existence of a threshold in the weight loss or degree of metabolic improvement that is necessary to resolve NASH. In fact, the probability of reaching the primary endpoint increased non-linearly above 20% weight reduction and further decreases in bodyweight above this threshold translated into less additional histological improvement. Resolution of NASH was also associated with postoperative improvement of insulin resistance and triglyceride concentrations. A threshold mechanism for changes in insulin resistance might explain the lower effect of further weight reduction above 20% and the lack of differences observed between Roux-en-Y gastric bypass and sleeve gastrectomy.

Type 2 diabetes was the only baseline variable that negatively predicted NASH resolution without progression of fibrosis. This finding is consistent with previous observations showing that type 2 diabetes is a major risk factor for NAFLD and that the condition significantly increases the likelihood of developing NASH in comparison with the non-diabetic population.[23] An estimated 18·2 million people in the USA live with type 2 diabetes and NAFLD, of whom 6·4 million have NASH.[24]

A study investigating the effect of weight loss achieved through diet and physical exercise on liver histological features was done in 293 people with NASH.[5] NASH resolution was reached in 25% of the participants and 19% had regression of liver fibrosis.[5] The 1-year mean weight loss in the study was 4·6 kg (SD 3·2); however, only 10% had a weight loss of 10% or greater.[5] Comparatively, the mean weight loss in the lifestyle-intervention group of this study was 5·5% and only 27% achieved a weight reduction of at least 10%. These findings provide reassurance regarding the effectiveness of lifestyle modification in our study, thus providing an appropriate comparator for the related effectiveness of surgical therapy.

Studies show that new anti-obesity medications (eg, tirzepatide[9] or cagrilintide plus semaglutide[25]) can achieve levels of weight loss close to 20% in some people, suggesting that these drugs might be more effective as a treatment of NASH compared with lifestyle modification, as well as with pioglitazone and liraglutide, the drugs used in our study. Semaglutide achieved resolution of NASH without fibrosis worsening in 59% of participants versus 17% in the placebo group in one trial.

Importantly, however, there was no difference in previous studies between semaglitude and placebo in the downstaging of liver fibrosis,[10] despite the substantial weight loss achieved by this drug. This observation suggests that the net improvement of fibrosis achieved by surgery in our study might not be extrapolated to other forms of weight-loss interventions. The relative efficacy of newer anti-obesity drugs on NASH and liver fibrosis will therefore require further investigation.

The ITT analysis showed that in participants with an NAFLD activity score of 4 or 5 or more, the probability of reaching the primary endpoint was 3–5 times higher with bariatric-metabolic surgery than with lifestyle modification. In this subgroup, the improvement of at least one stage of fibrosis in the per protocol analysis was almost double after both Roux-en-Y gastric bypass and sleeve gastrectomy than after lifestyle modification. The ability of surgery to control and even improve fibrosis associated with NASH is of particular clinical relevance given that fibrosis is the main predictor of liver complications and cardiovascular mortality and morbidity in NASH.[26,27]

The number of surgical complications in our study was similar after both surgical procedures. Several participants had gastro-oesophageal reflux after sleeve gastrectomy. Gastro-oesophageal reflux disease is a known complication of sleeve gastrectomy;[28] the high rate of gastro-oesophageal reflux disease in our study might partly be related to a more frequent use of

postoperative diagnostic endoscopy compared with in usual clinical practice, which is a standard practice in postoperative assessment of patients undergoing sleeve gastrectomy at our centres.

A cost-effectiveness analysis[29] of bariatric-metabolic surgery in individuals with NASH showed that surgery is cost-effective in all individuals with obesity and NASH, regardless of fibrosis stage, making surgery a suitable approach for the treatment of this condition.

Previous studies had shown efficacy of bariatric-metabolic surgery on NAFLD.[30–32] Our study supports these findings and also provides evidence that benefits of surgery extend to NASH and liver fibrosis.. Our results have important implications for clinical practice. There are no existing mechanisms for prioritisation of bariatric-metabolic surgery in most health-care systems and access to surgery is often based on a first-come-first-served basis.[33] Our study supports prioritisation of surgery in NASH, especially in the presence of a high risk of liver-related morbidity and mortality. A study of 30 000 individuals with NAFLD and BMI of 40 kg/m² or more showed that bariatric surgery conferred a 49% lower risk of cardiovascular disease compared with non-surgical care.[34] Whether or not surgery could be used as a treatment of NASH in patients who do not meet standard criteria for bariatric-metabolic surgery cannot be extrapolated from our study and warrants further and specific investigation.

Our study is the first to compare three active treatments of NASH and investigate the efficacy of bariatric-metabolic surgery in a randomised trial. Importantly, this study used preoperative and postoperative liver biopsy, which is the gold standard for assessment of NASH-related endpoints.[6]

This study has several limitations. First, our protocol was designed before the FDA guidance[6] was published recommending the use of an NAFLD activity score of at least 4 with at least 1 point each in inflammation and ballooning along with a CRN fibrosis score of 2–3 as essential inclusion criteria in NASH trials. In the present study, we included people with an NAFLD activity score of at least 3, and inflammation and ballooning scores in line with the most recent FDA guidance. However, consistent with most NASH trials published since 2021 our study included people with fibrosis stages 1–3.[10,35]

To investigate the effect of interventions according to the most recent FDA recommendations, we did a post-hoc analysis of the primary endpoint in participants with an NAFLD activity score of 4 or at least 5. We also did subgroup analyses of results in participants with fibrosis stages 2 and 3, who accounted for more than 50% of all participants in our study. In the aggregate, the results of these subgroup analyses show that differences between surgical and non-surgical treatment of NASH are greater among participants with more severe fibrosis. This finding supports the robustness of the overall findings of our study and their clinical relevance in patients with more advanced stages of fibrosis.

As our study did not control for baseline BMI and glycaemic control, differences in bodyweight and diabetes severity at baseline could have, at least partly, influenced the response to treatment. However, BMI and HbA_{1c} levels were higher in the Roux-en-Y gastric bypass group, which would potentially bias results against rather than in favour of surgery, which was the most effective intervention. Another limitation is that the medications used reflect indications and drugs available in Italy for people with obesity and NASH at the time the study was designed. Novel anti-obesity drugs might result in better NASH outcomes than those we observed in the non-surgical group of our study, given their greater weight-loss potential. Future research should compare new anti-obesity drugs with other active drugs or bariatric-metabolic surgery. Another important limitation is that all participants in this study were White, meaning that the rates of NASH resolution and other metabolic improvements observed in this trial might not be generalisable to other ethnic groups.

Contributors

GM, OV, SP, SRB, and MR designed the study. SP did the statistics. GA did the analyses. LC-G, OV, EL, EC, CG, LS, FP, JRC-M, PM, IB, and GC carried out the study. MP, LR, and MAZ performed liver biopsies and hepatological follow-up. FMV read all liver biopsies and JRCM reread the biopsies. GM, OV, SP, MR, ADG, IB, EF, SRB, and FR analysed results and wrote the manuscript. All authors actively contributed to the definitive version. GM and SP accessed and verified the data, and all authors had access to the data.

Declaration of interests

GM reports consulting fees from Novo Nordisk, Fractyl, and Recor. She is also scientific adviser for Metadeq, Keyron, GHP Scientific, and Jemyll, these all being unpaid positions. FR reports receiving research grants from Ethicon and Medtronic; receiving consulting fees from Novo Nordisk, Ethicon, and Medtronic; serving on the scientific advisory board of and receiving consultancy fees from GI Dynamics; and is a former director and current scientific advisor of Metadeq, Keyron, and GHP Scientific, these all being unpaid positions. All other authors declare no competing interests.

Data sharing

The data collected for our study will be made available upon reasonable request.

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