**TITLE PAGE:**

**Title:**

Bariatric surgery for patients with type 2 diabetes mellitus requiring insulin: clinical outcome and cost-effectiveness analyses

**Short title:**

Clinical and cost-effectiveness of bariatric surgery in patients with severe T2DM

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ABSTRACT

## **Background:**

Although bariatric surgery is well established as an effective treatment for patients with obesity and type 2 diabetes (T2DM), there exists reluctance to increase its availability for patients with severe T2DM. The aim of this study was to examine the impact of bariatric surgery on diabetes resolution in patients with obesity and T2DM requiring insulin (T2DM-Ins) using data from a national database, and to develop a health economic model to evaluate the cost-effectiveness of surgery in this cohort when compared to best medical treatment.

## **Methods and findings:**

Clinical data from the National Bariatric Surgical Registry (NBSR), a comprehensive database of bariatric surgery in the United Kingdom (UK), were extracted to analyze outcomes of patients with obesity and T2DM-Ins who underwent primary bariatric surgery between 2009 and 2017. Two thousand four hundred and eighty-four patients were eligible for inclusion, of which 1847 had one-year follow up data. Outcomes for this group were combined with data sourced from a comprehensive literature review in order to develop a state-transition micro-simulation model to evaluate cost-effectiveness of bariatric surgery versus best medical treatment (BMT) for patients over a 5-year time horizon. The main outcome measure for the clinical study was insulin cessation at one-year post-surgery: relative risks (RR) summarising predictive factors were determined, unadjusted, and after adjusting for variables including age, initial BMI, duration of T2DM and weight loss. Main outcomes measures for the economic evaluation were total costs, total quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) at willingness-to-pay threshold of £20,000.

Sixty-seven per cent of patients no longer required insulin at one-year post-operatively: these rates persisted for four years. RYGB was associated with a better rate of insulin cessation (71.7%; p<0.001) than SG (64.5%; RR 0.92, CI 0.86-0.99) and AGB (33.6%; RR 0.45, CI 0.34-0.60). When adjusted for percentage total weight loss and demographic variables, insulin cessation following surgery was comparable for RYGB and SG (RR 0.97, CI 0.90-1.04), with AGB having the lowest cessation rates (RR 0.55, CI 0.40-0.74; p<0.001). Over 5 years, bariatric surgery was cost-saving compared to BMT (total cost £22,057 vs £26,286 respectively, incremental difference £4229). This was due to lower treatment costs as well as reduced diabetes-related complications costs, and increased health benefits. Our study has some limitations, including loss to follow-up of patients within the NBSR dataset.

## **Conclusions:**

In this study we observed that in patients with obesity and T2DM-Ins, bariatric surgery is associated with high rates of post-operative cessation of insulin therapy, which is in turn a major driver of overall reductions in direct healthcare cost. Our findings suggest that a strategy utilising bariatric surgery for patients with obesity and T2DM-Ins leads to a return of investment within 3 years.

AUTHOR SUMMARY

Why was this study done?

* Bariatric or weight loss surgery can dramatically improve type-2 diabetes (T2DM) in patients with obesity, allowing many patients to stop medicines for T2DM completely.
* Unfortunately, there are limited resources for performing bariatric surgery. Patients with severe T2DM, who require daily insulin injections, are at risk of being considered lower priority than those with T2DM managed by tablet medications. This is because some small studies have suggested that that T2DM requiring insulin is too advanced to be reversed by surgery.
* The aims of this study were to see how effective bariatric surgery is in patients with obesity and T2DM requiring insulin, as well as to determine if performing surgery in this group is cost-effective over a 5-year period.

What did the researchers do and find?

* We used data from a nationwide registry of patients undergoing bariatric surgery in the UK to examine the effect of surgery on patients that require insulin for T2DM. We found that certain types of procedure (Roux en Y gastric bypass and sleeve gastrectomy) were associated with excellent rates of stopping insulin (approximately 2/3 of patients).
* We then devised an economic model to compare the costs of this type of surgery with the costs of treating patients using the best available medicines for T2DM. We found that performing surgery cost less money in total, over a 5-year timeline.

What do these findings mean?

* These findings are important because they suggest that patients with obesity and T2DM requiring insulin are good candidates for bariatric surgery.
* Offering bariatric surgery to such patients could save money as well as improving their health.

# **MAIN TEXT**

# **Introduction:**

Over the last decade bariatric surgery has been shown to be an effective treatment for type 2 diabetes mellitus (T2DM) in patients with obesity [1,2]. Surgery is associated with superior improvement in hyperglycaemia as compared to best medical treatment, an effect that is sustained for at least five years [3-6]. The improvement in hyperglycaemia is associated with a reduction in mortality [7,8] and diabetes-related complications [9,10]. Improvement in T2DM following bariatric surgery is mediated by both weight loss-dependent and weight loss-independent mechanisms [11,12].

T2DM is however a progressive, heterogenous disorder with a spectrum of severity [13,14]. To date, the major randomised controlled trials investigating the clinical outcomes of bariatric surgery for T2DM have focused predominantly on patients with more recent onset disease not requiring insulin, as opposed to patients with disease of longer duration requiring insulin [3,4]. To date, there has only been one study, a regional registry analysis, focused on patients who require insulin for their T2DM [15]. A number of retrospective studies have analysed the factors associated with successful diabetes remission following bariatric surgery [16-18]. These studies suggest that patients with more severe T2DM (defined as requiring insulin treatment and/or of long duration) are less likely to experience sustained remission of hyperglycaemia following bariatric surgery. These disappointing findings may explain unsupportive attitudes exhibited by some clinicians or policymakers towards surgical treatment for patients with obesity and longer standing T2DM requiring insulin (T2DM-Ins): the national commissioning guidelines in Scotland, for example, permit referral for bariatric surgery only for patients with new-onset T2DM (less than five years) [19].

In addition to the clinical benefits of bariatric surgery for individual patients with obesity and T2DM, a number of studies have analysed the healthpayer costs of bariatric surgery [20-22]. Although these studies suggest that surgery is cost-effective as compared to medical management, to date no economic evaluations focus on patients with T2DM-Ins. Moreover many of these existing economic analyses pre-date the wide scale adoption of newer anti-diabetic medications such as glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium-glucose transport protein 2 (SGLT2) inhibitors - medications which have recently changed the landscape of treatment for patients with more severe T2DM [23]. Though effective, these new medications have significant cost implications. There is a need, therefore, to investigate the clinical outcomes of bariatric surgery in a large cohort of patients with T2DM-Ins and evaluate the cost-effectiveness of a surgical strategy in this cohort.

The purposes of this study were two-fold: firstly, to evaluate clinical outcomes following bariatric surgery in patients with obesity and T2DM-Ins using a United Kingdom (UK) registry dataset which represents the largest cohort published to date; and secondly, to combine the data with other relevant sources to develop a model-based economic evaluation to assess the cost and cost-effectiveness of bariatric surgery versus best medical treatment (BMT) in this cohort.

Methods:

The clinical study analysis and cost-effectiveness study framework were planned at the time of study conception. For the clinical study this included the variables that would be adjusted for during regression analysis. For the cost-effectiveness analysis, the model was designed, and data inputs agreed prior to running the model: these data inputs would include those derived from previous studies as well as the present clinical study. This study is reported as per the CHEERS guideline (S1 CHEERS Checklist).

Design of the clinical study

Data source and study population

To evaluate the clinical outcomes of patients with obesity and severe T2DM, as well as prognostic factors predictive of clinical outcomes, we extracted data from the National British Surgical Registry (NBSR). The NBSR is a bespoke database for the prospective collection of demographic, peri-operative and clinical outcome data for patients with obesity undergoing bariatric surgery in the United Kingdom and Republic of Ireland [24]. The details of the demographic and clinical data recorded in this database as well as the data quality are detailed in previous publications [25,26]. Fully anonymised data were extracted from the registry from patients that had previously consented to the collection of their data. The data holder NBSR complied with local ethics guidelines and use of this dataset for research purposes conformed with UK legislation and was approved by the Health Research Authority (17/CAG/0023).

Diabetes status in NBSR is recorded pre-operatively and at every post-operative visit as follows: no indication of T2DM; impaired glycaemia or impaired glucose tolerance (diet-controlled); oral hypoglycaemics only; or insulin treatment (insulin with or without additional hypoglycaemic medications). As insulin use has consistently been identified as a strong negative predictor of remission of T2DM after bariatric surgery [16-18], we focused on patients that were using insulin for T2DM pre-operatively (T2DM-Ins).

From the database we identified all patients with T2DM-Ins who had undergone primary Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) or adjustable gastric band (AGB) between 1st January 2009 and 31st May 2017. As the majority of patients have several follow-up episodes recorded on NBSR, data were selected as follows: for outcomes at one year, only patients with a follow-up appointment between 6- and 24-months post-surgery were included, and data were extracted from the clinic appointment closest to the one year point after surgery; for longer-term outcomes, data were extracted from the final recorded clinic appointment, with exclusion of any patients with less than two years’ follow up. For diabetes status over time, all patients with any follow-up visit were included.

Analytical approach

Data are presented as mean with standard deviation, or number with percentage of total in parentheses.

Percent weight loss (%WL) was calculated as percent of total weight lost using the following formula:

% WL = 100 x (Follow up Weight – Initial Weight) / Initial Weight

Percent excess weight loss (%EWL) was calculated based on an optimum body mass index (BMI) of 25kg/m2, using the following formula:

% EWL = 100 x (Follow up BMI – Initial BMI) / (Initial BMI – 25)

Comparison of baseline factors and outcomes by procedure was initially carried out by analysis of variance (means), quantile regression (medians) or chi-square tests as appropriate. Further adjusted comparison of factors predicting insulin cessation following surgery were made using Poisson regression to generate relative risk ratios, 95% confidence intervals and p values (PROC GENMOD, SAS version 9.4). Robust standard errors were estimated accounting for clustering by hospital, and an offset term was included based on follow-up time. For procedure type, RYGB was chosen as the reference category. Baseline factors used for adjustment were age, gender, initial BMI, smoking, number of co-morbidities, duration of diabetes and ethnicity. Additionally, a further model adjusted for post-operative change in weight (with initial BMI removed), in order to assess any potential contributions to improvement in T2DM mediated through weight loss independent mechanisms of the different operations. This analysis was included because it has been demonstrated that some bariatric procedures (such as RYGB) may be associated with greater weight loss-independent improvements in T2DM as compared to others [11,12]. Age and weight-related variables (BMI, weight loss and excess weight loss) are presented within categories, but additional models were fitted with them as continuous variables.

Design of the health-economic model

We developed a model-based management protocol in order to compare the costs and effects of a strategy of surgical intervention versus best medical management (BMT) for patients with obesity and T2DM-Ins, over a 5-year timeline horizon. As detailed in full in S1 Text, individual patients with T2DM-Ins were simulated based on characteristics from the UK NBSR dataset and then duplicated to create an identical clone. In the model, one clone was treated with BMT while the other was treated with bariatric surgery. This strategy ensures that the treatment comparisons are not being influenced by differences in patient characteristics, but only based on the treatments received. Each clone or ‘patient’ was then put through the model, and the costs and health outcomes were summed for all patients in each treatment arm. The model is developed as a state-transition patient level simulation with 1-year cycle length.

Model inputs

The data from the NBSR as presented in this paper were utilised to inform baseline patient characteristics for the population (see ‘Model Inputs’, S1 Text).

For the purposes of this evaluation, given the inferior efficacy of AGB when compared to RYGB and SG in T2DM improvement (see results below) we modelled that patients in the surgical group would only undergo either RYGB or SG. We assumed, based on recent UK procedure prevalence data [27], that 58% would undergo RYGB and 42% SG.

The BMT regimen (which includes nutritional counselling) was determined from the latest guidelines from the American Diabetes Association and European Association for Study of Diabetes and expert consensus (see S1 Text) [23]. All costs and outcomes after the first year were discounted 3.5% per year in line with NICE recommendations.

The model is fully described in S1 Text, including the sources from which all model inputs were derived.

Model outcomes

The model calculates the following outcomes:

1. Total costs (consisting of direct treatment costs, cost of adverse events, and cost of disease- related complications)
2. Life-years gained
3. Quality-adjusted life year (QALY), an outcome that captures life expectancy and quality of life in one measure; and cost per QALY
4. Incremental costs: the difference in the total cost between bariatric surgery and BMT
5. Incremental QALYs: the difference in the total QALYs gained between bariatric surgery and BMT
6. Incremental cost-effectiveness ratio (ICER), which is calculated by dividing the difference in cost between two arms (incremental cost) by the difference in QALYs (incremental QALYs). In general, the treatment option is considered cost-effective when the incremental cost-effectiveness ratio (ICER) is below a willingness-to-pay threshold of £20,000/QALY [28].
7. Net monetary benefit (NMB): the value of bariatric surgery in monetary terms under the willingness-to-pay threshold of £20,000/QALY for a unit of benefit. It is calculated as NMB= Δ QALY\*λ – Δ cost, where λ is willingness to pay threshold in England (GBP 20,000/QALY). Intervention is considered cost-effective when NMB is greater than zero.
8. Net health benefit (NHB): the value of bariatric surgery in terms of health benefit corrected for the incremental costs divided by willingness to pay threshold. NHB is calculated as NHB= Δ QALY - Δ Cost/λ. Treatment is considered cost-effective when NHB is greater than zero. Both NMB and NHB are presented at willingness-to-pay thresholds of £20,000/QALY.
9. Probabilistic sensitivity analysis-cost-effectiveness plane, which reports an average ICER with a 95% confidence interval and the probability that the intervention is cost-effective.

Results:

Clinical study

Description of cohort

Three thousand two hundred and sixty-one surgical patients with T2DM-Ins were identified from the NBSR as having had primary RYGB, SG or AGB during the designated time frame (Fig 1). Of these, 2,484 (76.2%) had at least one follow-up visit recorded in the NSBR, with 1,847 having one visit between 6- and 24-months post-surgery (“one-year follow up”). Of these, 1313 (71.1%) underwent RYGB, 397 (21.5%) SG, and 137 (7.4%) AGB. Demographic data for these patients is summarized in Table 1.

**Fig 1. Flow chart to illustrate selection of surgical patients from NBSR database for the clinical study**

Primary procedures were defined as Roux-en-Y gastric bypass, sleeve gastrectomy or adjustable gastric band. Acceptable data required all the following: non-zero age, initial weight 70-400kg, height 1-2m and duration of T2DM recorded.

**Table 1:** **Baseline demographic data for surgical patients by procedure (n=1,847)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | All | AGB | SG | RYGB |
| Number of patients | n (%) | 1,847 (100) | 137 (7.4) | 397 (21.5) | 1,313 (71.1) |
| Age (years) | mean (sd) | 51.1 (9.4) | 52.6 (9.6) | 52.2 (10.1) | 50.7 (9.1) |
| Initial Weight (kg) | mean (sd) | 132.7 (24.5) | 130.1 (21.8) | 138.3 (28.8) | 131.2 (23.0) |
|  | median (IQR) | 131.0 (115.3-148.1) | 129.0 (113.8-143.6) | 134.7 (119.0-153.6) | 129.9 (115.0-145.8) |
| Initial BMI (kg/m2) | mean (sd) | 47.2 (7.3) | 47.0 (6.3) | 49.1 (8.7) | 46.6 (6.9) |
|  | median (IQR) | 46.3 (41.8-51.5) | 46.9 (41.8-51.5) | 47.7 (42.8-54.4) | 46.1 (41.6-50.7) |
| Sex |  |  |  |  |  |
| - Men | n (%) | 667 (36.1) | 44 (32.1) | 156 (39.3) | 467 (35.6) |
| Smoking\* |  |  |  |  |  |
| - Never | n (%) | 984 (56.1) | 62 (49.6) | 238 (63.0) | 684 (54.7) |
| - Ex | n (%) | 642 (36.6) | 51 (40.8) | 116 (30.7) | 475 (38.0) |
| - Current | n (%) | 127 (7.2) | 12 (9.6) | 24 (6.4) | 91 (7.3) |
| Duration of T2DM |  |  |  |  |  |
| - 0 to 5 years | n (%) | 454 (24.6) | 29 (21.2) | 100 (25.2) | 325 (24.8) |
| - 6 to 10 years | n (%) | 568 (30.8) | 42 (30.7) | 116 (29.2) | 410 (31.2) |
| - >10 years | n (%) | 825 (44.7) | 66 (48.2) | 181 (45.6) | 578 (44.0) |
| Number of co-morbidities |  |  |  |  |  |
| - 0 | n (%) | 525 (28.4) | 42 (30.7) | 112 (28.2) | 371 (28.3) |
| - 1 | n (%) | 623 (34.2) | 45 (32.9) | 133 (33.5) | 454 (34.6) |
| - 2 or more | n (%) | 690 (37.4) | 50 (36.5) | 152 (38.3) | 488 (37.2) |
| Ethnicity\* |  |  |  |  |  |
| - White | n (%) | 1,591 (90.4) | 125 (94.0) | 328 (87.0) | 1,138 (91.0) |
| - Non-White | n (%) | 169 (9.6) | 8 (6.0) | 49 (13.0) | 112 (9.1) |

\* Expressed among those with a recording in each category. Missing data for the following categories: n=94 (5.1%) had no smoking data record, n=87 (4.7%) had no ethnicity recorded. sd = standard deviation; IQR = interquartile range.

Clinical outcomes

At one-year follow up (mean of 355 days post procedure) the mean percentage weight loss was 27.4%, with evidence of differential weight loss between surgical groups (p<0.001; Table 2).

Overall, approximately one-third (32.7%) of the total cohort were still using insulin at 1 year, with another third (33.5%) no longer recorded as having T2DM. There was significant variation in T2DM status by procedure (p<0.001); with 33.6% having ceased use of insulin in the AGB group compared to 64.5% and 71.7% in the SG and RYGB groups respectively, and a smaller proportion of patients assessed as having no indication of T2DM following AGB (5.1%) than SG and RYGB (30.0% and 37.6% respectively).

**Table 2:** **Outcomes for surgical patients at 1 year by procedure (n=1,847)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | All (n=1,847) | AGB (n=137) | SG (n=397) | RYGB (n=1,313) | p-value\*\* |
| Days since procedure | mean (sd) | 354.7 (89.1) | 362.6 (80.0) | 351.2 (91.5) | 354.9 (89.2) | 0.43 |
| Re-admission within 30 days\* |  |  |  |  |  |  |
| - No | n (%) | 1,718 (94.5) | 127 (94.8) | 374 (95.4) | 1,217 (94.2) | 0.64 |
| - Yes | n (%) | 100 (5.5) | 7 (5.2) | 18 (4.6) | 75 (5.8) |  |
| Weight Loss |  |  |  |  |  |  |
| - %WL | mean (sd) | 27.4 (9.3) | 15.8 (9.0) | 25.1 (9.2) | 29.4 (8.2) | <0.001 |
|  | median (IQR) | 27.6 (21.6-33.6) | 15.5 (10.3-21.3) | 24.9 (19.3-30.4) | 29.5 (24.1-34.8) | <0.001 |
| - %EWL | mean (sd) | 61.5 (22.9) | 35.0 (20.1) | 54.7 (22.8) | 66.3 (20.8) | <0.001 |
|  | median (IQR) | 60.6 (47.0-75.3) | 34.6 (21.8-49.7) | 53.0 (39.8-67.4) | 64.9 (52.7-78.7) | <0.001 |
| Diabetes Status |  |  |  |  |  |  |
| - No indication of T2DM | n (%) | 619 (33.5) | 7 (5.1) | 119 (30.0) | 493 (37.6) | <0.001 |
| - Impaired Fasting Glycemia | n (%) | 77 (4.2) | 4 (2.9) | 19 (4.8) | 54 (4.1) |  |
| - Oral Hypoglycaemics | n (%) | 548 (29.7) | 35 (25.6) | 118 (29.7) | 395 (30.1) |  |
| - Insulin | n (%) | 603 (32.7) | 91 (66.4) | 141 (35.5) | 371 (28.3) |  |

\*Missing data for n=29 (1.6%) patients \*\* P-value for tests of heterogeneity between procedure type (ANOVA, comparison of medians using quantile regression or chi-square test) Sd = standard deviation, IQR = interquartile range.

Follow-up of over 2 years (mean 1132 days, maximum 3274 days) was available for 857 patients of whom 605 (70.6%) underwent RYGB, 156 (18.2%) SG and 96 (11.2%) AGB (Table 3). Weight loss varied again by procedure (p<0.001) with levels broadly similar to what was reported at one-year follow-up. For diabetes status, differences between procedures were still apparent (p<0.001), with a wider gap now seen at 2 years between the percentage of patients with no indication of T2DM in the RYGB (42.2%) and SG (26.9%) groups.

**Table 3: Outcomes for surgical patients at final post 2 year follow up by procedure (n=857)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | All | AGB | SG | RYGB | p-value\* |
| Number of patients | N (%) | 857 (100) | 96 (11.2) | 156 (18.2) | 605 (70.6) |  |
| Days since procedure | mean (sd) | 1131.5 (466.9) | 1455.2 (551.3) | 1062.8 (413.6) | 1097.9 (445.3) | <0.001 |
| Weight Loss |  |  |  |  |  |  |
| - %WL | mean (sd) | 27.1 (11.1) | 17.2 (10.0) | 24.7 (11.5) | 29.3 (10.1) | <0.001 |
|  | median (iqr) | 27.3 (19.5-34.9) | 17.0 (10.8-24.2) | 23.5 (17.4-32.2) | 29.1 (22.6-36.3) | <0.001 |
| - %EWL | mean (sd) | 59.7 (25.0) | 37.7 (22.6) | 53.3 (26.1) | 64.9 (22.8) | <0.001 |
|  | median (iqr) | 59.3 (43.6-76.6) | 36.5 (24.3-51.0) | 51.0 (35.7-70.1) | 64.4 (49.8-80.2) | <0.001 |
| Diabetes Status |  |  |  |  |  |  |
| - No indication of T2DM | n (%) | 314 (36.6) | 17 (17.7) | 42 (26.9) | 255 (42.2) | <0.001 |
| - Impaired Fasting Glycemia | n (%) | 40 (4.7) | 3 (3.1) | 10 (6.4) | 27 (4.5) |  |
| - Oral Hypoglycaemics | n (%) | 270 (31.5) | 24 (25.0) | 50 (32.1) | 196 (32.4) |  |
| - Insulin | n (%) | 233 (27.2) | 52 (54.2) | 54 (34.6) | 127 (21.0) |  |

\* P-value for tests of heterogeneity between procedure type (ANOVA, comparison of medians using quantile regression or chi-square test) Sd = standard deviation, IQR = interquartile range.

Fig 2 summarises T2DM status over 4 years, in 3-month periods, for all surgical patients with follow-up within those periods only. Prevalence of insulin use reached a plateau at around 19-24 months, stabilising at this level up to 4 years after surgery. Similarly, BMI reached a plateau at around 13-18 months, stabilising over the next four years (Fig 3).

**Fig 2: Type 2 diabetes mellitus (T2DM) status in patients over time since bariatric procedure**

Percentage of patients with each T2DM status amongst those with a follow-up visit during each time period from bariatric procedure. Numbers at each visit were: month 0-6 n=2,150; month 7-12 n=1,446; month 13-18 n=1,114; month 19-24 n=639; month 25-30 n=633; month 31-36 n=251; month 37-42 n=190; month 43-48 n=108.

**Fig 3: Body mass index (BMI) in patients over time since bariatric procedure**

Box and whisker plot (median and IQR) to illustrate BMI of patients amongst those with a follow-up visit during each time period from bariatric procedure. Whiskers represent the upper and lower adjacent values, with dots showing observations beyond these values. Numbers at each visit were: month 0-6 n=2,133; month 7-12 n=1,442; month 13-18 n=1,112; month 19-24 n=637; month 25-30 n=633; month 31-36 n=250; month 37-42 n=189; month 43-48 n=108.

### *Prediction of insulin cessation by baseline factors*

Insulin cessation was more prevalent in patients undergoing RYGB than in patients undergoing SG (RR 0.92, 95%CI 0.86-0.99, p=0.02) or AGB (RR 0.45, 95%CI 0.34-0.60, p<0.001) (table 4). Male patients were more likely to cease insulin use after surgery (RR 1.14, 95%CI 1.07-1.23, p<0.001). There was no evidence of different insulin cessation rates by number of co-morbidities (RR 1.02, 95% 0.94-1.11 for 2 or more versus none). Patients with shorter T2DM duration were more likely to cease insulin (RR 1.40, 95%CI 1.29-1.53, p<0.001, for patients with duration <5 years as compared to those with duration >10 years). When adjusted for other baseline demographic factors, procedure, gender and duration of diabetes were all independent predictors of cessation of insulin use after surgery (p<0.001).

**Table 4**: **Unadjusted and adjusted relative risks for insulin cessation at follow-up by baseline factors (n=1,847)**

|  | **N** | **% on Insulin at 6-24 mo. follow-up** | **RR (95% CI) Unadjusted** | **RR (95% CI) Mutually adjusted** |
| --- | --- | --- | --- | --- |
| Operation Type |  |  |  |  |
| - AGB | 137 | 66.4% | 0.45 (0.34-0.60) | 0.46 (0.35-0.61) |
| - RYGB | 1,313 | 28.3% | 1 | 1 |
| - SG | 397 | 35.5% | 0.92 (0.86-0.99) | 0.91 (0.84-0.98) |
| p-value\* |  |  | <0.001 | <0.001 |
| Age (years) |  |  |  |  |
| - 17 to 39 | 222 | 35.6% | 0.89 (0.81-0.98) | 0.90 (0.83-0.97) |
| - 40 to 49 | 540 | 30.4% | 1 | 1 |
| - 50 to 59 | 718 | 31.9% | 0.95 (0.87-1.04) | 0.98 (0.90-1.06) |
| - 60 + | 367 | 35.7% | 0.91 (0.81-1.01) | 0.97 (0.88-1.07) |
| p-value† |  |  | 0.96 | 0.13 |
| Sex |  |  |  |  |
| - Female | 1,180 | 35.9% | 1 | 1 |
| - Male | 667 | 26.8% | 1.14 (1.07-1.23) | 1.14 (1.06-1.23) |
| p-value\* |  |  | <0.001 | <0.001 |
| Initial BMI |  |  |  |  |
| - 40 or less | 284 | 34.5% | 1.04 (0.89-1.22) | 1.02 (0.87-1.19) |
| - 40 to 45 | 479 | 35.3% | 1 | 1 |
| - 45 to 50 | 490 | 32.0% | 1.04 (0.95-1.13) | 1.02 (0.94-1.11) |
| - 50 to 55 | 324 | 31.2% | 1.05 (0.96-1.14) | 1.03 (0.95-1.12) |
| - 55 to 60 | 176 | 31.8% | 1.09 (0.96-1.23) | 1.10 (0.98-1.24) |
| - 60 or more | 94 | 23.4% | 1.14 (0.99-1.32) | 1.11 (0.96-1.27) |
| p-value† |  |  | 0.31 | 0.31 |
| Smoking |  |  |  |  |
| - Never | 984 | 32.4% | 1 | 1 |
| - Ex vs. Never | 642 | 32.9% | 1.01 (0.94-1.08) | 1.00 (0.93-1.07) |
| - Current vs. Never | 127 | 25.2% | 1.12 (1.01-1.23) | 1.09 (0.98-1.27) |
| p-value\* |  |  | 0.051 | 0.10 |
| Co-Morbidities |  |  |  |  |
| - 0 | 525 | 36.2% | 1 | 1 |
| - 1 | 632 | 30.2% | 1.06 (0.98-1.16) | 1.07 (1.00-1.15) |
| - 2 or more | 690 | 32.2% | 1.02 (0.94-1.11) | 1.03 (0.95-1.12) |
| p-value\* |  |  | 0.70 | 0.50 |
| T2DM Duration (years) |  |  |  |  |
| - 0 to 5 | 454 | 19.8% | 1.40 (1.29-1.53) | 1.39 (1.28-1.50) |
| - 6 to 10 | 568 | 27.3% | 1.31 (1.19-1.44) | 1.29 (1.17-1.42) |
| - >10 years | 825 | 43.4% | 1 | 1 |
| p-value\* |  |  | <0.001 | <0.001 |
| Ethnicity |  |  |  |  |
| - White | 1,591 | 32.4% | 1 | 1 |
| - Non-white | 169 | 32.5% | 1.06 (0.96-1.18) | 1.09 (1.00-1.20) |
| p-value\* |  |  | 0.40 | 0.21 |

\* - p-values test for heterogeneity between categories, † - p-values test for linear trend derived from model where age and BMI were fitted as continuous variables.

### *Prediction of insulin cessation by subsequent change in weight*

Lower %WL and %EWL at follow up was associated with significantly poorer rates of insulin cessation (table 5). To investigate whether the relative improvement in insulin cessation outcomes conferred by RYGB was related to weight loss, the model was fitted adjusting for all baseline factors except initial BMI, with either %WL (WL model) or %EWL (EWL model) included. Once weight loss was adjusted for using either model, SG was no longer associated with statistically inferior rates of insulin cessation compared to RYGB (RR 0.97, 95%CI 0.90-1.04, p=0.37 for WL model, and RR 0.97, 95%CI 0.91-1.04, p=0.44 for EWL model). Even when adjusted for weight loss, however, AGB was still associated with poorer rates of insulin cessation than RYGB (RR 0.55, 95%CI 0.40-0.74 for WL model and RR 0.56, 95%CI 0.42-0.73 for EWL model, p<0.001).

**Table 5:** **Unadjusted and adjusted relative risks for insulin cessation at follow-up by subsequent change in weight and procedure (n=1,847)**

|  | **N** | **% on Insulin at 6-24 mo. follow-up** | **RR (95% CI) Unadjusted** | **RR (95% CI) Fully Adjusted\* (WL model)** | **RR (95% CI) Fully Adjusted\* (EWL model)** |
| --- | --- | --- | --- | --- | --- |
| Operation Type |  |  |  |  |  |
| - AGB | 137 | 66.4% | 0.45 (0.34-0.60) | 0.55 (0.40-0.74) | 0.56 (0.42-0.73) |
| - RYGB | 1,313 | 28.3% | 1 | 1 | 1 |
| - SG | 397 | 35.5% | 0.92 (0.86-0.99) | 0.97 (0.90-1.04) | 0.97 (0.91-1.04) |
| p-value\* |  |  | <0.001 | <0.001 | <0.001 |
| Weight Loss (%) |  |  |  |  |  |
| - 20% or less | 369 | 51.5% | 1 | 1 | \_ |
| - 20 to 25% | 335 | 36.4% | 1.33 (1.17-1.52) | 1.21 (1.06-1.38) | \_ |
| - 25 to 30% | 407 | 31.9% | 1.45 (1.27-1.66) | 1.33 (1.16-1.51) | \_ |
| - 30 to 35% | 359 | 23.7% | 1.55 (1.36-1.78) | 1.37 (1.20-1.57) | \_ |
| - 35% or more | 377 | 20.2% | 1.53 (1.34-1.74) | 1.35 (1.19-1.54) | \_ |
| p-value† |  |  | <0.001 | <0.001 |  |
| Excess Weight Loss (%) |  |  |  |  |  |
| - 25% or less | 75 | 68.0% | 0.51 (0.39-0.67) | \_ | 0.64 (0.51-0.80) |
| - 25 to 50% | 471 | 40.6% | 1 | \_ | 1 |
| - 50 to 75% | 825 | 30.7% | 1.16 (1.06-1.27) | \_ | 1.13 (1.04-1.22) |
| - 75 to 100% | 388 | 22.4% | 1.26 (1.15-1.39) | \_ | 1.19 (1.09-1.30) |
| - 100% or more | 88 | 23.9% | 1.22 (1.04-1.43) | \_ | 1.19 (1.00-1.40) |
| p-value† |  |  | <0.001 |  | <0.001 |

\* - p-values test for heterogeneity between categories, † - p-values test for linear trend derived from model where Weight Loss and Excess Weight Loss were fitted as continuous variables.

To assess whether non-linearity between age, %WL, %EWL and insulin cessation would impact the RR for insulin cessation conferred by the different operations, sensitivity analyses fitted alternative models using quadratic terms: these adjusted models generated approximately the same RRs, consistently finding AGB to be inferior to RYGB and SG for insulin cessation (S1 Table).

Cost and cost-effectiveness analysis

Detailed results are presented in S1 Text. S2-15 Tables detail model inputs, S16 Table provides additional results and S17-19 Tables give uncertainty and scenario analyses. S1-S3 Fig illustrate model design and patient flow through the models, while S4 and S5 Fig provide additional results. The most important economic-related outcomes are summarised and presented below.

Direct costs

Table 6 summarises the results in terms of cumulative average treatment acquisition cost per patient over five years for surgery and BMT. Every patient in the bariatric surgery arm will follow the bariatric surgery costs (S10 Table), whereby their first-year treatment will have one-off surgery costs and subsequent drug costs. Every patient in the BMT arm will have drug costs as detailed in S11 Table which may vary each year, depending on whether treatment strategy stays the same (if HbA1C falls below 8) or is modified (S5 Table). If a patient dies before the end of the five- year term (from diabetes-related deaths or other deaths), they will no longer contribute to the acquisition costs or any other costs (see S2 Fig for patient flow).

As shown, when compared to best medical treatment (BMT), bariatric surgery leads to a direct cost saving over a five-year time horizon.

**Table 6: Treatment costs of surgery versus BMT costs**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Bariatric surgery | Best medical treatment | Incremental cost (BS-BMT) |
| **Drug costs (£)** | 641 | 10,578 | -9937 |
| **Surgery cost** | 5,544 | 0 | 5,544 |
|  |  |  |  |
| **Total treatment costs (£)** | 6,185 | 10,578 | -4,393 |

Adverse events

In relation to costs directly attributable to adverse events of treatment (i.e. in the surgical arm costs of surgical complications plus adverse drug reactions; and in the BMT group the adverse drug reactions) the cumulative costs for the bariatric surgical group were £1,152 and for the group undergoing BMT £955. This represents an incremental difference of £197 in favour of BMT over a five-year period.

Reductions in disease-related complications

Based on the assumptions of the effects of BMT and bariatric surgery on modifying HbA1C and BMI (both of which were the two most important predictors of T2DM complications, see S1 Text), bariatric surgery leads to a lower cumulative incidence of diabetes-related complications (Table 7) and consequently lower cost for the management of these complications (Table 8).

**Table 7: Predicted diabetes-related complications incidence**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Bariatric surgery | Best medical treatment | Incremental difference (BS-BMT) |
| Cumulative incidence of diabetes-related complications | | | |
| IHD | 3.17% | 4.12% | -0.95% |
| MI | 6.02% | 6.62% | -0.60% |
| CHF | 2.36% | 6.43% | -4.07% |
| Stroke | 1.63% | 2.06% | -0.43% |
| Amputation | 0.29% | 0.67% | -0.38% |
| Renal Failure | 0.42% | 0.35% | 0.07% |

IHD = ischaemic heart disease; MI = myocardial infarction; CHF = chronic heart failure

**Table 8: Cumulative cost of diabetes-related complications**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Bariatric surgery | Best medical treatment | Incremental difference (BS-BMT) |
| IHD cost | 414 | 542 | - 128 |
| MI cost | 381 | 362 | 19 |
| CHF cost | 187 | 491 | - 304 |
| Stroke cost | 283 | 352 | - 69 |
| Amputation cost | 55 | 113 | - 58 |
| Renal Failure cost | 197 | 144 | 52 |
| Non -hospital costs\* | 13,203 | 12,748 | 455 |
|  |  |  |  |
| **Total cost** | 14,720 | 14,753 | -33 |

IHD = ischaemic heart disease; MI = myocardial infarction; CHF = chronic heart failure

Summary of total costs

In summary, bariatric surgery results in direct cost saving of £4,229 when compared to BMT over a five-year time horizon according to the model predictions (Table 9).

**Table 9: Total costs of bariatric surgery and BMT over 5 years**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Bariatric surgery | Best medical treatment | Incremental difference (BS-BMT) |
| Treatment costs (£) | 6,185 | 10,578 | -4,393 |
| Adverse event costs (£) | 1,152 | 955 | 197 |
| Cost of complications (£) | 14,720 | 14,753 | -33 |
|  |  |  |  |
| **Total costs (£)** | 22,057 | 26,286 | -4,229 |

Unlike medication costs, the costs of surgery are incurred at the start of the model and not spread over the five year period, hence at approximately 3.5 years after surgery, the total cost of a patient treated with bariatric surgery equals the total cost of a patient treated with BMT, whereby from that break-even point, bariatric surgery becomes the cost-saving option.

Cost effectiveness

As shown in Table 10, from a cost effectiveness perspective, bariatric surgery leads to a lower cumulative incidence of diabetes-related complications and consequently improves life expectancy and quality of life.

Probabilistic sensitivity analysis demonstrated that bariatric surgery consistently leads to cost-savings when compared with BMT, and in more than 50% of cases to positive incremental health benefits (Table S16 and S5 Fig).

**Table 10: Cost-effectiveness of bariatric surgery and BMT over 5 years**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Bariatric surgery | Best medical treatment | Incremental difference (BS-BMT) |
| Costs (£) | 22,057 | 26,286 | -4,229 |
| Average QALYs | 3.18 | 3.15 | 0.03 |
| Life years gained in 5 years | 4.47 | 4.43 | 0.04 |
| NMB |  |  | 4,731 |
| NHB |  |  | 0.24 |
| ICER (cost/QALY) |  |  | Dominated by bariatric surgery\* |

QALY: Quality-adjusted life year; NMB: net monetary benefit; NHB: net health benefit; ICER: Incremental cost-effectiveness ratio. \*Dominated is a health economic term that describes an intervention which is more beneficial and less costly for patients.

Discussion:

This study demonstrates that bariatric surgery in patients with obesity and T2DM-Ins is associated with good medium-term clinical outcomes and is cost-saving when compared to best medical management both in terms of “upfront” treatment costs and avoidance of future costs of complications. In this, the largest clinical series to date, two-thirds of patients with T2DM-Ins at baseline ceased use of insulin after surgery, with one-third ceasing all medication for T2DM. Our data suggest that these improvements persist for at least four years following surgery. These results are comparable to those of a regional database study which reported that 27% of patients on insulin at baseline continued to take insulin at 3 years post-RYGB, with 40% off all medication for T2DM [15]. Interestingly, our results are also similar to those reported for patients with both recent and long standing T2DM: in a randomised controlled trial five years post-RYGB or SG, 35% of surgical patients had stopped taking all medications for T2DM [4]. Our findings therefore challenge the popular (but poorly-evidenced) view that bariatric surgery has limited clinical efficacy for patients with more advanced T2DM [14].

Our data indicate that in patients requiring insulin for T2DM, AGB is associated with lower rates of insulin cessation and remission of T2DM than RYGB and SG. Greater weight loss has been associated with superior T2DM outcomes [16,29]; and we found that this holds true for patients with T2DM-Ins. Moreover, even when adjusted for weight loss, AGB was associated with lower rates of insulin cessation when compared to RYGB or SG. These findings support the notion that improvements in T2DM seen after bariatric surgery have both weight loss-dependent and weight loss-independent components [12,30]. We observed a trend towards increased insulin cessation over time in the RYGB group, despite weight stability, suggesting a possible late weight loss-independent effect of RYGB on T2DM.

The major novel finding of this study is that over a five-year time horizon, the costs of bariatric surgery are predicted to be lower than those of medical management for patients with T2DM-Ins. Of particular note, the greatest savings stem from direct treatment costs: bariatric surgery is significantly cheaper than the medications that would otherwise be prescribed to patients with severe T2DM over a five-year period. This is an important finding, given that the majority of previous economic evaluations concluded that the direct treatment costs of surgery exceeded those of BMT [21,31-33]. The difference may be explained by the fact that previous studies either pre-dated the widespread adoption of newer pharmacological agents for diabetes, or focused on patients with early T2DM who are often maintained on relatively inexpensive single oral agents [20-22].

In terms of adverse events, our financial allocations for surgical complications over the five-year period are comparable to other models derived from UK data [20,22]; however, the majority of previous studies evaluating the costs of bariatric surgery versus medical management have not included costings for adverse events related to treatment in the medically treated patients [20,21]. The newer medications in use for T2DM such as GLP-1 RA and SGLT-2 inhibitors have side-effect profiles that require medical attention and treatment in a proportion of patients [34,35]. Though these adverse medical events do have cost implications, the adverse events costs for surgical patients are still slightly higher than for patients treated with BMT in this study.

With regard to avoidance of complications, previous economic evaluations have demonstrated contradictory results. In the UK, Gulliford et al demonstrated that although a bariatric surgical strategy in patients with obesity and T2DM had higher expected cost than medical management, the cost of subsequent clinical gains was sufficiently low to make surgery cost-effective to a health-care payer (£7129/quality-adjusted life year gained) [20]. By contrast, Borisenko et al found that the avoidance of complications through a surgical strategy in patients with obesity and T2DM lead to direct health care savings [22]. This saving however occurred over a long-time horizon (for female patients 10 years; and for male patients over a life-time). We have demonstrated that not only are there cost savings within the cohort of patients with T2DM-Ins due to avoidance of future complications, but these savings occur over a very short time horizon of less than five years. It is likely that the differences between our study findings and previous analyses are due to the fact that our study was designed to specifically investigate the sub-cohort of patients with T2DM requiring insulin, for whom BMT involves expensive medications.

Our study has some limitations. The NBSR dataset contains limited long-term follow up. We attempted to address this issue by mandating a minimum follow up period and limiting our procedure-specific analysis to 2 years after surgery. Moreover, it should be noted that loss to follow up rate in this study is comparable to other national registry studies (e.g. [15]) and there is no evidence of any systematic bias with regard to the outcomes of those who did and did not attend follow up. Furthermore, it should be noted that the total number of patients with T2DM-Ins with 4-year follow-up in the present study is larger than any previously published study. With regard to the comparison of the individual procedures, this was not a randomised controlled trial and hence there were significant size disparities (as well as potentially clinical and demographic differences) in the cohorts of patient undergoing AGB, SG and RYGB. In addition the NBSR does not include details on the dosage and number of medications that the patients took before and after surgery; however, it should be noted that the classification of diabetes status in the database is likely to have underestimated the efficacy of surgery as some patients in remission of diabetes are placed on prophylactic metformin [36]. Finally, we have not analyzed the impact of other procedures such as loop gastric bypass as this was infrequently performed at the time the data were collected.

With regard to the health economic model, we accept that the lack of HbA1c data in the NBSR cohort is a significant limitation as it does introduce a degree of uncertainty in our estimates of future diabetes-related complications. In the present study, changes in HbA1c levels post-surgery in our model were inferred from previous studies. Nonetheless, HbA1c levels may be less economically important than changes in medications, particularly given our finding that the direct medication costs in the BMT group (as opposed to changes in disease-specific complication rates) are the most significant factor in the cost-saving associated with bariatric surgery. As with all models, ours was unable to include all variables that may impact on overall outcomes. For example, our model was not designed to consider the broader cost implications of weight loss and improvement in T2DM status on occupational productivity. Additionally, we were unable to incorporate the potential differential effects of bariatric surgery as compared to BMT on lifestyle factors such as physical exercise and mental health status, which may in turn affect health and cost outcomes more broadly. Finally, our time horizon perspective for cost-effectiveness was deliberately short at five years, and therefore there is uncertainty around long term cost-effectiveness.

In summary this study provides evidence that a strategy of treating patients with obesity and T2DM-Ins with SG or RYGB is associated with a significant incidence of diabetes remission and a high incidence of cessation of insulin therapy. Moreover, while previous economic analyses have suggested that a surgical strategy for T2DM provides clinical benefits but with higher up-front cost to the health care payer, this study indicates that for patients with T2DM-Ins, the total cost to the health payer is reduced following bariatric surgery as compared to BMT over a 5-year time period. This pattern is seen even when the clinical benefits of bariatric surgery over BMT, in terms of avoidance of future complications, are not considered.

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SUPPORTING FILES

**S1 CHEERS Checklist**

**S1 Text. Supplementary methods and results for cost-effectiveness analysis**

**S1 Table. Adjusted relative risks for insulin cessation at follow-up by baseline factors in alternative models (n=1,847).**

\* - Model adjusts for same covariates as Table 4 but for age now fits the following terms: age, age2

† - Models adjust for same covariates as Table 5 but for age fits the following terms: age, age2 and in WL model fits %WL and %WL2, or in EWL model fits %EWL and %EWL2.

**S2 Table. Additional patient baseline characteristics**

**S3 Table. Treatment effect of bariatric surgery on HbA1c**

**S4 Table. Treatment effect of bariatric surgery on BMI**

**S5 Table. Best medical treatment (BMT) regimen.** Regimen agreed following discussion and unanimous consensus of panel of expert diabetologists: CWL, RB and GB.

**S6 Table. Treatment effect of BMTon HbA1c**

**S7 Table. Mid-term bariatric surgery complications**

**S8 Table. Adverse drug events for surgical patients.** \* % of patients with reduced drug dose and increase in HbA1c (not applicable after bariatric surgery)

**S9 Table.** **Annual incidence of adverse effects in BMT group.** \* % of patients with reduced drug dose and increase in HbA1c

**S10 Table. Direct costs in bariatric surgery group**

**S11 Table. Direct costs in BMT group**

**S12 Table.** **Cost of bariatric surgery complications**

**S13 Table.** **Costs of T2DM complications.** \* Weighted average of HRG AA35A, AA35B, AA35C, AA35D, AA35E, AA35F & Average of cost for 2–5 years

**S14 Table. Utilities and decrements associated with individual complications of T2DM.** All values from [21] except for Hypertension [22] and Hypoglycaemia [23]

**S15 Table. Decrements in utility associated with bariatric Surgery and BMI category**

**S16 Table. Additional model results**

**S17 Table. Probabilistic sensitivity analysis results (1,000 iterations)**

**S18 Table. Cost-effectiveness results for Afro-Caribbean population**

**S19 Table. Cost-effectiveness results for** **Indian-Asian population**

**S1 Fig. Arms of economic evaluation study**

**S2 Fig. Cost-effectiveness model flow**

**S3 Fig. Risk equations from the UKPDS Outcomes Model (UKPDS OM)**

**S4 Fig. Tornado diagram with most influential parameters in incremental cost between bariatric surgery and BMT**

**S5 Fig. Cost-effectiveness probability plan (PSA 1,000 iterations) for ICER (cost per QALY) bariatric surgery versus BMT**