The impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes: A matched controlled population-based retrospective cohort study

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Abstract

Aim: To assess the impact of bariatric surgery (BS) on incident microvascular complications [diabetes-related foot disease (DFD), sight threatening diabetic retinopathy (STDR), chronic kidney disease (CKD)] in patients with type 2 diabetes and obesity.

Methods: A retrospective matched, controlled population-based cohort study of adults with type 2 diabetes between 1/1/1990 and 31/1/2018 using IQVIA Medical Research Data (IMRD), a database of primary care electronic records. Each patient with type2 diabetes who subsequently had BS (surgical) was matched on index date with up to 2 patients with type 2 diabetes did not have BS (non-surgical) within the same general practice by age, sex, pre-index body mass index and diabetes duration.

Results: 1126 surgical and 2219 non-surgical participants were included. In the study population, 2261 (68%) were women; Mean (SD) age was 49.87 (9.3) vs 50.12 (9.3) years and BMI was 46.76 (7.96) kg/m^2 vs 46.14 (7.49) kg/m^2 in surgical vs non-surgical group respectively. In surgical group, 22.1%, 22.7%, 52.2% and 1.1% patients had gastric band, sleeve gastrectomy, gastric bypass & duodenal switch respectively.

Over median (IQR) follow-up was 3.9 years (1.8-6.4), BS was associated with reduction in incident combined microvascular complications (adjusted HR 0.63, 95% CI 0.51 to 0.78, $p<0.001$), DFD (0.61, 0.50 to 0.75, $p<0.001$), STDR (0.66, 0.44 to 1.00, $p<0.001$), CKD (0.63, 0.51 to 0.78, $p<0.001$). Analysis based on the type of surgery showed that all types of surgery were associated with favourable impact on the incident of composite microvascular complications, greatest reduction RYGB.

Conclusions: BS was associated with a significant reduction in incident diabetes-related microvascular complications.

Background

The rising levels of obesity and type 2 diabetes are major global health challenges. Vascular complications (microvascular and macrovascular) are the major causes of morbidity and mortality in patients with type 2 diabetes (1, 2).

Worldwide, the cost of health expenditure due to diabetes has increased from USD 232 billion in 2007 to USD 727 billion in 2017 and estimated to rise further to USD 825billion by 2030. The major portion of direct cost in diabetes management is spent in managing diabetes related complications and its consequences (2). The cost of diabetes management had been estimated to be 20 times more in patients with four or more diabetes related complications compared to patient with diabetes with no complications. (2). In the United Kingdom, diabetes accounts for 10% of the National Health Service (NHS) budget and 80% of this expense is spent dealing with diabetes-related complications mainly due to prolonged hospital stay, cardiovascular disease, kidney disease and neuropathy (3).

Despite improved clinical management of type 2 diabetes over the last 2 decades including new classes of glucose lowering medication (Dipeptidyl peptidase-4 inhibitor, sodium - glucose cotransporter2 inhibitor, glucagon like peptide-1 agonist) reduction in microvascular complications are far less compared to the reductions observed in cardiovascular disease (4). Diabetes-related foot disease (DFD) is the leading cause for non-traumatic lower limb amputation in the developed world (5); sight threatening diabetic retinopathy (STDR) is a leading cause of blindness at younger age (6), and diabetic nephropathy is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (7).

Obesity is an established risk factor for type 2 diabetes, hypertension and hyperlipidaemia (8). In addition, obesity is an independent risk factor for CKD (9), peripheral neuropathy (10-12), cardiovascular disease (13) and mortality (14). A number of studies have shown that intentional weight loss is associated with improvements in glycaemic control, blood pressure, hyperlipidaemia and other vascular risk factors (15, 16). Amongst the several interventions for the treatment of obesity, bariatric surgery (BS) provides the most significant and sustainable weight loss and has a favourable impact on glycaemic control and other vascular risk factors (17-19). We have recently shown that BS in patients with and without type 2 diabetes was associated with reduction in incident hypertension, cardiovascular disease and all-cause mortality compared to routine care (20). Hence, it would be expected that BS

surgery may also reduce the incidence of microvascular complications in patients with type 2 diabetes.

Currently, the impact of BS on diabetes-related microvascular complications remains unclear. A meta-analysis of 10 studies (3 RCTs and 7 controlled studies) involving 17532 patients found an overall reduction in incidences of retinopathy and nephropathy, but not neuropathy, in the surgical arm compared to the non-surgical arm; but there was heterogeneity in findings and in the definition of microvascular outcomes between the studies(21) . Hence there is lack of large, population-based studies examining the impact of BS on individual diabetes-related microvascular outcomes.

Our hypothesis was that BS is associated with a reduction in incidence of microvascular complications compared to routine care in people with type 2 diabetes and obesity.

We therefore conducted a population-based matched controlled cohort study to assess the impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes. We also examined the findings stratified by individual bariatric procedures.

Methods

Study design and data source

A retrospective matched controlled cohort study utilising IQVIA Medical Research Data (IMRD), database was conducted. IMRD is an electronic primary care database that includes longitudinal patient records of over 15 million patients, of which 3.7 million are currently active (contributing data to the database). The database covers around 6.2% of the UK population and has been shown to be representative of the UK demographic structure (22). IMRD contains demographic information, clinical diagnoses, procedures, laboratory results, medications, lifestyle information and every consultation episode with primary care. IMRD (previously referred as THIN database) has previously been used for research related to diabetes and vascular outcomes (23-27) and to assess effectiveness of bariatric surgery (20, 28).

Study population

Primary care practices were eligible for inclusion in the study if they had been using the Vision electronic records system for at least one year, and had Acceptable Mortality Reporting (an indicator of the practice data quality) for at last one year before study entry (29). In addition, study participants must have been registered with an eligible practice for at least one year before study entry. The above-mentioned criteria were to ensure data extracted

was high quality with adequate documentation of concomitant diseases and treatments. The surgical cohort were adult patients (18 years and above) with obesity (BMI ≥ 30 kg/m^2) who had type 2 diabetes and a subsequent record of a primary BS [gastric banding (GB), sleeve gastrectomy (SG), Gastric bypass (RYGB), duodenal switch (DS)]. Each patient with type 2 diabetes who had bariatric surgery (surgical) was matched on index date with up to 2 patients with type 2 diabetes who did not have bariatric surgery (non-surgical) within the same general practice by age (± 2 years), sex, pre-index body mass index (BMI, ±2 kg/m^2) and diabetes duration (± 3 years). Patients in the surgical group and their corresponding non-surgical were excluded from the study if they met any of the following criteria: had a BMI <30 kg/m^2, age >75 years, gastric balloon or endo-barrier or gastric cancer before bariatric surgery or had been coded as type 1 diabetes (Figure 1).

Follow-up

Index date for the surgical cohort was the date of bariatric surgery. For the non-surgical population, index date was assigned as the corresponding index date of their matched surgical patient to mitigate immortal time bias (30). Eligible participants were followed-up from the index date until the earliest occurrence of the following end points: a) incidence of the outcome of interest; b) death; c) patient left the practice; d) the practice ceased contributing to the database; or e) study end date (31/1/2018).

Outcome measures

The primary outcome measures were composite microvascular disease, DFD, STDR and CKD. Outcomes were defined by a rigorous process of clinical Read code selection (31), reviewing them against existing literature and ratifying through an expert panel of specialists in the field and primary care professionals.

DFD was defined as a composite of either foot ulcer, gangrene, deformity or amputation, moderate/high foot risk, peripheral vascular disease (PVD) or diabetes-related peripheral neuropathy (DPN) according to Read codes in the IMRD database (definition DFD1). Moderate foot risk was defined as presence of DPN, deformity or non-critical limb ischaemia. High foot risk was defined as previous ulcer, amputation, more than 2 of the 3 parameters of DPN, deformity or PVD (32, 33). We considered alternative definitions for DFD in the analysis. DFD2 was defined as any of the components of DFD1, not including PVD/ DPN codes. DFD3 was defined as any of the components of DFD2 without including moderate/high foot risk codes. In addition, we explored the risk of incident DPN and PVD separately, as secondary outcomes.

STDR was defined as either pre-proliferative retinopathy (R2), proliferative retinopathy (R3) or maculopathy (M1); retinopathy treatment (photocoagulation/vitreous injection); or vision loss (24). In a sensitivity analysis, we excluded vision loss from the outcome definition, as this may have been caused by pathologies other than diabetes such as macular degeneration or cataract.

CKD was defined as eGFR <60 ml/min/1.73m^2 or albuminuria (Albumin creatinine ratio, ACR ≥3mg/mmol) (34). In addition, we looked at eGFR <30 ml/min/1.73m^2 and macro-albuminuria (ACR >30 mg/mmol) separately. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate the eGFR value from the creatinine value (35). In sensitivity analysis, we defined two consecutive values of eGFR <60 ml/min/1.73m^2 and two consecutive ACR ≥3mg/mmol as outcomes. In both analyses, patients who had the outcome measure of interest before the index date were excluded.

All outcomes defined above are assessed annually as part of the Quality and Outcomes Framework (QOF) scheme in primary care and are therefore likely to be accurate; this regular assessment also mitigates surveillance bias (36).

Statistical analysis

Baseline characteristics were summarised as mean (±standard deviation, SD) or median (interquartile range, IQR) for continuous variables and proportions for categorical variables. Covariates in the adjusted/multivariable model were selected based on biological plausibility; these included age, sex, high BMI, smoking status, ethnicity, and social deprivation status, hypertension status, DM duration, baseline HbA1c and medications including ACE inhibitors, anti-lipid drugs and insulin. BMI (in kg/m^2) was categorised as <35 kg/m^2, 35-40 kg/m^2 and > 40 kg/m^2. Smoking were categorised as smoker, non-smoker, and ex-smoker. Social deprivation status was represented by Townsend deprivation quintile which is based on material deprivation within a population (31). Ethnicity was categorised as Caucasian, Afro-Caribbean, south Asian, mixed. A missing category was used for missing data for BMI, Townsend quintile, smoking status, and ethnicity. Hypertension status and medications were handled as binomial variable and age, DM duration and baseline HbA1c as continuous variables.

We calculated crude and adjusted hazard ratios (adjHR) and 95% confidence intervals (CIs) for the occurrence (incident) of each outcome of interest in the surgical versus non-surgical groups using a Cox proportional hazards regression model. Participants with the outcome of

interest in the surgical or non-surgical group at baseline were excluded from the respective analysis. For CKD analysis, we also excluded the patients on renal replacement therapy defined as patient with renal transplant or on dialysis at baseline.

The proportional hazards assumption was checked using the Schoenfeld residuals test. We adjusted for biologically plausible confounders as mentioned above.

Stratifying by type of surgery, we analysed the outcome in participants undergoing gastric band, sleeve gastrectomy and gastric bypass and their corresponding non-surgical control group. We did not perform analysis in the duodenal switch subgroup due to small numbers.

We know that beneficial effects of BS on weight loss and glycaemic control lessen overtime, so we reported the latest weight and HbA1c to avoid inflation of results in favour of surgery. Post-surgical weight was defined as latest weight available for surgical or non-surgical group after the index date and before the exit date. Percentage weight loss (%WL) was calculated as $\frac{post-surgical\ weight\ (latest\ available)-baseline\ weight}{baseline\ weight} \times 100$. For the non-surgical group who had no surgery, weight change was calculated using latest weight after the index date and baseline weight. Independent sample t-test was used to compare the %WL in surgical and non-surgical groups. HbA1c was standardized as a percentage (Diabetes Control and Complications Trial, DCCT unit). We calculated the change in HbA1c (latest HbA1c available after the index date minus baseline HbA1c) and used independent sample t-test to compare percentage difference between surgical and non-surgical groups.

We used Nelson-Aalen plots (non-parametric estimator) to present the cumulative hazard function for each outcome over 10-year periods. A two-tailed p-value <0.05 was considered statistically significant. All analyses were conducted using Stata version 15.

Results

Baseline characteristics

We included 1126 surgical and 2219 non-surgical participants. Baseline characteristics are summarised in Table 1. Mean (SD) age was 50 (9.3) years; and 2261 (67.59%) participants were women. Mean (SD) BMI was 46.76 (7.96) kg/m^2 vs 46.14 (7.49) kg/m^2 and mean (SD) HbA1c was 7.78% (1.82) vs 7.82% (1.69) for surgical vs non-surgical participants, respectively. Median (IQR) DM duration was 4.72 (2.17-8.93) vs 4.63 (1.91-8.19) years in surgical vs non-surgical participants. Most of the study population (88.9% of the surgical and 82.1% of the non-surgical) were not recorded as active smokers. Insulin was prescribed for

270 (23.98%) vs 315 (14.20%) of the surgical vs non-surgical participants, respectively. The prevalence of microvascular complications at baseline was similar in the surgical and non-surgical groups.

Out of 1126 participants in surgical group, 249 (22.1%), 255 (22.7%), 610 (52.2%) and 12 (1.1%) patients had GB, SG, RYGB and DS, respectively.

Weight change

Data on weight before and after index date was available for 1067 (94.8%) surgical and 1943 (87.6%) non-surgical participants. Over the median (IQR) follow-up of 2.8years (1.2- 4.9 years) in surgical vs 3.4 years (1.5- 5.6 years) in non- surgical group, surgical group achieved a greater %WL (mean, SD) of 21.6% (13%) compared to 4.6% (9.7%) in the non-surgical group.

Participants who underwent surgery lost more weight compared to their matched non-surgical for all surgical procedures: GB 14.6% (13.9%) vs 4.6% (10.3%), p<0.001; SG 20.6% (11.5%) vs 4.2% (10.1%), p<0.001; RYGB 25.0% (12.0%) vs 4.8% (9.1%), p<0.001; and DS 21.2% (10.8%) vs 1.7% (9.3%), p<0.001.

Glycaemic control

HbA1c values before and after index date were available for 1043 (93%) surgical and 1958 (88%) non-surgical participants. Over the median (IQR) follow-up period of 2.6 (1- 4.9 years) in surgical group vs 3.1 years (1.2- 5.5 years) in non- surgical group, participants in the surgical group achieved a mean reduction in HbA1c of 1.3% (95% CI 1.2-1.5) [14.2 mmol/mol, (13.1- 16.4)] while in non-surgical HbA1c increased by 0.2% (95% CI 0.1-0.3) [2.2 mmol/mol, (1.1- 3.3)]. The mean HbA1c reduction difference between surgical and non-surgical cohorts was 1.5% (95% CI 1.4-1.7) [16.4 mmol/mol (15.3- 18.5)]. Participants receiving any of the surgical procedures achieved greater HbA1c reductions compared to non-surgical with a mean reduction difference of 1% (95% CI 0.7-1.3) [10.9 mmol/mol (7.6-14.2] in GB, 1.4% (1.1-1.7) [15.3 mmol/mol (12.0- 18.5)] in SG, 1.8% (1.6-2.0) [19.6 mmol/mol (17.4- 21.8)] in RYGB and 2.4% (0.8-4.0) [26.2 mmol/mol (8.7- 43.6)] in DS.

Composite microvascular disease

BS was associated with 47% reduction in the hazard of developing composite microvascular complications vs. non-surgical (adjHR 0.53; 95% CI 0.43 to 0.66) over the median (IQR) follow up period of 2.2 year (1-4.4 year).

Analysis based on the type of surgery showed that all types of surgery were associated with favourable impact on the incident of composite microvascular complications. The adjHRs and follow up duration in each surgical procedure can be found in table 2.

Diabetes-related foot disease, peripheral neuropathy, and peripheral vascular disease

BS was associated with reduction in the hazards of incidence DFD1 by 39% ($p<0.001$).

Analysis based on the type of surgery showed that all types of surgery were associated with favourable impact on the incident of DFD1, but this reached statistical significance only in the RYGB and GB group, but not in SG group.(Table 2)

BS was associated with reduction in incidence DFD2 by 37% ($p<0.001$) and DPN by 28% ($p=0.037$). There was non-significant reduction in hazards of DFD3 and PVD in surgical group vs non-surgical group in adjusted analysis (Table 3)

Sight threatening diabetic retinopathy

Over the median (IQR) follow-up of 3.5 years (1.6-5.7), BS was associated with 34% reduction in incidence of STDR ($p=0.048$). In a sensitivity analysis excluding low vision/blindness in the outcome definition, we found a 42% reduction in incidence of STDR in the surgical group compared to the non-surgical group, ($p=0.021$) (Table 2).

Stratifying by the type of BS showed that there was a statistically significant decrease in incident STDR in the GB cohort vs their non-surgical, but no association was observed in SG or RYGB group (Table 2).

CKD

Over the median (IQR) follow-up of 2.7 years (1.1-4.9), there was a 37 % reduction in incident CKD in the surgical group compared to the non-surgical group, ($p<0.001$) (Table 2).

Examining the data based on the type of BS showed that all types of surgery were associated with favourable impact on incident CKD, but this was statistically significant in RYGB and SG, but not in GB (Table 2).

No significant association was observed between BS and incident eGFR <60 ml/min/1.73 m^2 or <30 ml/min /1.73 m^2 (Table 4).

There was a 40% reduction in incident albuminuria in the surgical group compared to the non-surgical group ($p<0.001$), and a 64% reduction in macroalbuminuria ($p=0.009$) (Table 4).

In a sensitivity analysis, the observed association of BS with reduction in incidence microalbuminuria defined with two consecutive measurements ACR ≥3mg/mmol persisted with adjHR of 0.52 (95% CI 0.37- 0.72). But no association of BS and incidence eGFR <60 ml/min/1.73 m^2(2 consecutive results) was found.

Nelson-Aalen cumulative hazard estimates for study outcomes

The cumulative hazard estimates for the study outcomes over a 10-year period can be found in Figure 2. The figure illustrates the association between BS and the reduction in incident composite microvascular complications, DFD1, STDR and CKD. The impact of BS on incident DFD1 and CKD was apparent within the first 2-3 years post-surgery while the impact on STDR took longer to become apparent (5-6 years).

Discussion

Our study provides real-world population-based data showing that BS was associated with significant reduction in incident composite microvascular complications, DFD, STDR, CKD and DPN in patients with type 2 diabetes compared to routine care, after accounting for many potential confounders. The association between BS and reduction in incident STDR took longer to become apparent compared to the other microvascular complications (Figure 2). In addition, bariatric surgery was associated with greater reductions in weight and HbA1c compared to routine care during the follow-up, with the greatest reductions observed in the gastric bypass and duodenal switch groups.

Our results are similar to other published findings but add novel aspects. Our group previously showed in a single centre matched controlled studies that over 3 years BS was associated with less estimated glomerular filtration (eGFR) decline (37) and incident maculopathy (38) compared to routine care; but these studies were of a small sample size, single centre, with limited number of patients.

Sheng et al also showed that BS was associated with lower risk of incident composite microvascular complications in a systematic review, but unlike our study there were no results based on individual microvascular complications (39).

The Swedish Obese Subject (SOS) study, a prospective matched controlled intervention study, showed a reduction in the incidence rate of composite microvascular complications in patients who had undergone BS (n=343) compared to controls (n=260) (18). However, there were limitations in that the majority surgical procedure performed was vertical gastroplasty, mean (±SD) diabetes duration in surgical group was short (mean 2.9 ±4.7) years), and there

was no assessment of individual microvascular outcomes. In addition, the SOS study started before many of the current type 2 diabetes interventions were established (such as the use of statins and ACEi/ARB).

Another study from the United States (US), with a similar design to our study, based on four integrated health systems, found that BS was associated with reduction in incident retinopathy, nephropathy and neuropathy (40). This study did not examine the impact of BS on STDR and the impact on nephropathy was measured only using eGFR and not albuminuria.

After BS, patients show a decrease in fat mass, as well as a loss of lean mass, including muscle mass (41, 42). Therefore, it is difficult to differentiate if change in creatinine level and creatinine-based eGFR is indicative of true improvement in renal function. However, in our study the association between surgery and reduction in incident CKD was mainly driven by reduction in albuminuria which is not affected by loss of muscle mass.

In another study of similar design from Denmark, RYGB was associated with reduction in the incidence of microvascular complications (CKD, retinopathy, and neuropathy) similar to what we observed in our study (HR 0.53 [95% CI 0.38, 0.73) (43). But in this study, they did not report the outcomes of individual microvascular complications and our study adjusted for more variables in the Cox regression analysis (such as Townsend social deprivation index).

The Longitudinal Assessment of Bariatric Surgery (LABS) Study examined the impact of RYGB and GB over a follow up period of up to seven years and found beneficial effect on weight loss, diabetes and hypertension status (44). While this was a study conducted in general population with obesity, our study was specifically focused on people with type 2 diabetes and reported on comprehensive outcomes of multiple vascular complications.

LABS-Teen specifically reported the impact of BS on CKD in adolescents with type 2 diabetes with a sample size of 30. No other microvascular complications were analysed. (45). Our study was specific in adults, included multiple bariatric procedures, had a larger sample size, and reported on DFD and STDR.

We have recently shown using the IMRD database that BS was associated with reduction in incident CVD, hypertension, and mortality in patients with and without diabetes (20). Taken together with the findings of this study, this suggests that BS can play an important role in reducing the burden of type 2 diabetes by reducing the incidence of hypertension, CVD,

microvascular disease and mortality as well as significant improvements in weight and glycaemic control. These benefits were observed despite that more patients in surgical group had insulin treatment at baseline. Furthermore, in addition to reducing the personal burden of type 2 diabetes, the observed potential benefits are likely to have significant savings in health care costs considering the high cost of diabetes-related macro- and micro-vascular complications (3) . Despite these potential benefits in people with type 2 diabetes, access to BS is limited in most western health care systems; improving access to BS in patients with type 2 diabetes might therefore have positive implications for diabetes care (46).

There are several plausible mechanisms for the observed beneficial effects of BS on incident microvascular complications. It is likely that BS exerts its beneficial effects by improving the established risk factors for microvascular complications including weight, HbA1c, blood pressure, lipids, and CVD (19, 47, 48). In addition, recent data suggest that BS can result in sodium glucose co-transporter 2 (SGLT2) inhibition (49) and several studies previously showed that BS is associated with increased incretin and GLP-1 responses (50). These could contribute to the improved vascular outcomes after BS considering the latest cardiovascular outcomes trials in type 2 diabetes showing that GLP-1 receptor agonists and SGLT2 inhibitors can reduce CVD and CKD (51-53).

We managed to conduct subgroup analysis by type of procedure which added novelty to our study. We showed that all types of surgery included in this study were associated with reduction in the incidence of composite microvascular complications vs. the non-surgical arm. However, there was some variation in the relationship between the type of surgery and individual microvascular outcomes. GB had a favourable impact on DFD and STDR but not CKD; SG had a favourable impact on CKD only; and RYGB had a favourable impact on CKD and DFD but not STDR. These observations are not fully understood as yet and requires further evaluation.

We could not find any studies comparing the impact of different bariatric procedures on microvascular diseases as we did in our study. Based on the systematic review by Billeter et al (published in 2018) (21), only 3 studies included all types of surgery in same study (18, 38, 54). However, none of these papers reported the outcomes based on type of surgery and only Johnson et al papers reported on individual microvascular complications again no subgroup analysis by types of surgery was reported

Limitations and strengths:

The main limitation of our study is its observational nature, and hence causation cannot be proven. However, we used matching and extensive adjustments to account for confounding. Participants with the outcome of interest at baseline were excluded from the analysis due to methodological considerations. Therefore, any effect of BS in patients who already have microvascular complications requires future research. C-peptide data was not available in our study dataset as it is not yet a routine care test in United Kingdom; however, we included the information on diabetes duration and baseline insulin user and adjusted our outcomes for these variable. We had a short follow up period duration.

Our study has several strengths: we used a validated primary care data source (the IMRD database) and used previously by our team (23-27) and other researchers to explore similar outcomes (55, 56). Using IMRD allowed us to include a large sample size, matched with non-surgical, and adjust for several covariates improving the generalisability of our findings. Furthermore, the outcomes of our study were measured as part of the Quality Outcome Framework (QOF) on an annual basis ensuring consistency in definitions and mitigating against detection bias.

Conclusion

BS was associated with a reduction in microvascular complications, including DFD, STDR, CKD and DPN, in patients with type 2 diabetes and obesity. Improving access to BS could reduce the burden of type 2 diabetes; and access to surgery needs to be improved

Ethics

Use of IMRD is approved by the UK Research Ethics Committee (reference number: 18/LO/0441); in accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (in January 2019, reference number: 18THIN097). IMRD incorporates data from The Health Improvement Network (THIN), A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care.

Copyright Statement

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Author contributions:

AAT, PS and KN had the original idea for the study. PS, AAT, and KN designed the study. KG undertook data extraction. PS designed and performed the analysis, which was reviewed by KN, AS and NA. PS, AS, KN and AAT contributed to the data analysis and interpretation. PS wrote the first draft of the paper, which was revised and edited by NA, SB, KAT, RS, KG, AAT and KN. PS, AAT and KN affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. PS and KN had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Baseline characteristics of participants in the surgical and non- surgical groups

	Surgical	Non- surgical
Population, n	1126	2219
Age		
Age Categories, years, n (%)		
<41	171 (15.19)	329 (14.83)
41-60	803 (71.31)	1568 (70.66)
61-max	152 (13.50)	322 (14.51)
Mean (SD)	49.87 (9.3)	50.12 (9.3)
Sex, n (%)		
Male	366 (32.50)	718 (32.36)
Female	760 (67.50)	1501 (67.64)
BMI Categories		
<35	57 (5.06)	121 (5.46)
35- 39.9	165 (14.65)	344 (15.50)
>=40	901 (80.02)	1748 (78.77)
Missing	3 (0.27)	6 (0.27)
Mean (SD)	46.76 (7.96)	46.14 (7.49)
Smoker categories, n (%)		
Non-Smoker	563 (50.00)	1189 (53.58)
Smoker	125 (11.10)	395 (17.80)
Ex-Smoker	438 (38.90)	633 (28.53)
Missing	0 (0)	2 (0.09)
Drinker Categories, n (%)		
Non-drinker	315 (27.98)	625 (28.17)
Drinker	688 (61.10)	1403 (63.23)
Ex- Drinker	74 (6.57)	92 (4.15)
Missing	49 (4.35)	99 (4.46)
Ethnicity, n (%)		
Caucasian	620 (55.06)	1094 (49.30)
Black Afro-Caribbean	25 (2.22)	37 (1.67)
South Asian	32 (2.84)	56 (2.52)
Mixed Race	7 (0.62)	10 (0.45)
Other	2 (0.18)	9 (0.41)
Missing	440 (39.08)	1013 (45.65)
Townsend, n (%)		
1 (Least deprivation <20%)	185 (16.43)	250 (11.27)
2	178 (15.81)	290 (13.07)
3	219 (19.45)	463 (20.87)
4	234 (20.78)	492 (22.17)
5 (Most deprived >80%)	160 (14.21)	414 (18.66)
Missing	150 (13.32)	310 (13.97)
Baseline comorbidities		
Mental Health Conditions, n (%)		
Anxiety	310 (27.53)	526 (23.70)

Depression	616 (54.71)	1001 (45.11)
Cardiovascular Diseases, n (%)		
Hypertension	620 (55.06)	1239 (55.84)
Atrial Fibrillation	26 (2.31)	47 (2.12)
Heart Failure	16 (1.42)	46 (2.07)
Ischemic Heart Disease	74 (6.57)	165 (7.44)
Stroke/TIA	30 (2.66)	70 (3.15)
OSA	243 (21.58)	175 (7.89)
DM duration Median (IQR)	4.72 (2.17-8.93)	4.63 (1.91-8.19)
Insulin user n (%)	270 (23.98)	315 (14.20)
Baseline Microvascular complications		
Any microvascular complication (DFD3/STDR/CKD)	649 (57.64)	1220 (54.98)
DFD1	350 (31.08)	633 (28.53)
DFD2	212 (18.83)	371 (16.72)
DFD3	61 (5.42)	106 (4.78)
DPN	155 (13.77)	291 (13.11)
PVD	126 (11.19)	226 (10.18)
STDR	57 (5.06)	151 (6.80)
CKD	481 (42.72)	865 (38.98)

DFD1-=ulcer or gangrene or deformity or amputation or Moderate/high foot risk or DPN/PVD

DFD2= ulcer or gangrene or deformity or amputation or Moderate/high foot risk

DFD3= ulcer or gangrene or deformity or amputation

PN= Peripheral neuropathy

PVD= Peripheral vascular disease

STDR- Site threatening diabetic retinopathy

CKD= Chronic kidney disease (eGFR<60 ml/min/1.73 m^2 or Albumin: creatinine ratio≥3

Table 2: Incidence of composite microvascular complications and diabetic foot disease (DFD), diabetic retinopathy (STDR) and nephropathy in total population and subgroup analyses

	Composite microvascular complications		DFD1		STDR		CKD	
	Surgical	Non- surgical	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical
Population, n	477	999	776	1586	1069	2068	645	1354
Outcome events, n (%)	116 (24.3)	420 (42.0)	125 (16.1)	396 (25.0)	34 (3.2)	96 (4.6)	113(17.5)	385(28.4)
Person-years	1478.6	2768.3	2681.7	5271.4	4014.3	8205.3	2108.4	4378.2
Crude IRR	78.45	151.72	46.61	75.12	8.47	11.7	53.6	87.94
Follow up	2.4 (1- 4.4)	2.1 (1-4.3)	3.0 (1.3- 5.2)	2.8 (1.3- 5.0)	3.3 (1.5- 5.5)	3.6 (1.5- 5.9)	2.7 (1.1- 4.9)	2.7 (1.1- 5.0)
Crude HR (95% CI), p- value	0.52 (0.42-0.64), <0.001		0.62 (0.51- 0.76), <0.001		0.72 (0.49-1.07), 0.105		0.61 (0.49-0.75), <0.001	
Adj HR (95% CI), p-value	0.53 (0.43-0.66), <0.001		0.61 (0.50- 0.76), <0.001		0.66 (0.44-1.00), 0.048		0.63 (0.51-0.78), <0.001	
Gastric banding								
	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical
Population, n	133	240	188	366	240	465	165	308
Outcome events, n (%)	49 (36.8)	127 (52.9)	39 (20.7)	119 (32.5)	12 (5.0)	36 (7.7)	51 (30.9)	121(39.3)
Person-years	514.4	845.9	895.3	1521.9	1223.4	2399.5	692.5	1287.2
Crude IRR	95.25	150.13	43.56	78.19	9.81	15	73.65	94
Follow up	3.5 (1-6.2)	2.7 (1.3-5.6)	4.3 (2- 7.2)	3.8 (1.8- 6.3)	4.9 (2.3- 7.5)	5.2 (2.6- 7.5)	4.1 (1.4- 6.5)	3.7 (1.8- 6.4)
Crude HR (95% CI), p- value	0.64 (0.46- 0.89), 0.008		0.55 (0.39- 0.80), 0.001		0.65 (0.34- 1.25), 0.194		0.77 (0.55- 1.06), 0.112	
Adj HR (95% CI), p-value	0.65 (0.46- 0.91), 0.013		0.53 (0.36- 0.78), 0.001		0.49 (0.24- 0.99), 0.048		0.77 (0.55- 1.09), 0.144	
Sleeve gastrectomy								
	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical
Population, n	104	206	165	335	241	456	147	283

Outcome events, n (%)	21 (20.2)	73 (35.4)	27 (16.4)	76 (22.7)	6 (2.5)	12 (2.6)	17 (11.6)	65 (23)
Person-years	299.07	439.21	484.73	926.2	782.32	1521.87	425.9	756.58
Crude IRR	70.22	166.21	55.7	82.06	7.67	7.89	39.92	85.91
Follow up	2.3 (1- 4.0)	1.6 (0.7- 3.6)	2.4 (0.9- 4.3)	2.3 (1- 4.1)	2.8 (1.3- 5)	2.8 (1.2- 4.9)	2.2 (1- 4.2)	2 (0.9- 4.0)
Crude HR (95% CI), p- value	0.45 (0.27- 0.73), 0.001		0.69 (0.44-1.07), 0.098		1 (0.376-2.69, 0.989		0.47 (0.27- 0.80), 0.005	
Adj HR (95% CI), p-value	0.49 (0.29- 0.83), 0.008		0.70 (0.44- 1.11), 0.13		1.41 (0.49- 3.99), 0.523		0.52 (0.29- 0.91), 0.023	
Gastric bypass								
Population, n	236	542	413	869	577	1123	329	748
Outcome events, n (%)	44 (18.6)	220 (40.6)	57 (13.8)	201 (23.1)	16 (2.8)	48 (4.3)	44 (13.4)	197(26.3)
Person-years	656.1	1446.46	1277.87	2775.225	1978.4	4206.25	979.26	2288.854
Crude IRR	67.06	152.1	44.61	72.43	8.087	11.41	44.93	86.069
Follow up	2.2 (1- 4.2)	1.9 (0.9- 4.1)	2.6 (1.3- 4.4)	2.8 (1.3- 4.8)	3.0 (1.5- 5.0)	3.5 (1.6- 5.6)	2.5 (1- 4.4)	2.5 (1- 4.8)
Crude HR (95% CI), p- value	0.44 (0.32- 0.61), <0.001		0.61 (0.46- 0.82), 0.001		0.72 (0.41-1.27), 0.255		0.52 (0.38- 0.72), <0.001	
Adj HR (95% CI), p-value	0.42 (0.30- 0.59), <0.001		0.58 (0.43-0.79), 0.001		0.63 (0.35-1.16), 0.137		0.51 (0.36- 0.71), <0.001	

DFD1= ulcer/ gangrene/ deformity/ amputation /Moderate or high foot risk/ Peripheral neuropathy/ Peripheral vascular disease; STDR- Site threatening diabetic retinopathy; IRR= Incidence Rate/1000 person-years; Crude HR=Unadjusted Hazard Rate ratio

Adj HR= Adjusted Hazard Rate ratio; Adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration and baseline HbA1c and medications including ACE inhibitors, anti-lipid drugs and insulin.

Table 3: Incidence of diabetic foot disease (DFD2 & DFD3), peripheral neuropathy and peripheral vascular disease

	DFD2		DFD3		DPN		PVD	
	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical
N	914	1848	1065	2113	971	1928	1000	1993
Outcome events, n (%)	147 (16.1)	453 (24.5)	29 (2.7)	64 (3.0)	58 (6.0)	157 (8.1)	29 (3.0)	81 (4.1)
Person-years	3314.8	6488.0	4028.9	8457.09	3590.71	7308.73	3642.73	7667.25
Crude IRR	44.35	69.82	7.2	7.57	16.15	21.48	7.96	10.56
Follow up	3.3 (1.5- 5.4)	3.0 (1.4- 5.3)	3.3 (1.6- 5.5)	3.6 (1.6- 6.0)	3.2 (1.5- 5.4)	3.4 (1.5- 5.7)	3.2 (1.5- 5.4)	3.5 (1.6- 5.6)
Crude HR (95% CI), p-value	0.63 (0.53- 0.76), <0.001		0.96 (0.62- 1.48), 0.841		0.63 (0.53- 0.76), <0.001		0.75 (0.49- 1.15), 0.185	
Adj HR (95% CI), p-value	0.63 (0.52- 0.76), <0.001		0.87 (0.55- 1.37), 0.538		0.63 (0.52- 0.76), <0.001		0.70 (0.45- 1.09), 0.113	

DFD2 = amputation/ ulcer/gangrene/ deformity/moderate/high foot risk
DFD3 = amputation/ ulcer/gangrene/ deformity
DPN= Peripheral neuropathy; PVD= Peripheral vascular disease
IRR= Incidence Rate/1000 person-years; Crude HR=Unadjusted Hazard Rate ratio
Adj HR= Adjusted Hazard Rate ratio; Adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration and baseline HbA1c and medications including ACE inhibitors, anti-lipid drugs and insulin.

Table 4: Incidence of eGFR <60 ml/min per 1.73 m^2, eGFR <30 ml/min per 1.73 m^2, ACR≥3mg/mmol, and ACR>30mg/mmol and sensitivity analysis

	eGFR		ACR	
	Surgical	Non-surgical	Surgical	Non-surgical
Population, n	963	1931	737	1510
	eGFR <60		**ACR≥3**	
Outcome events, n (%)	67 (6.96)	174 (9.01)	109 (14.79)	372 (24.64)
Person-years	3482.7	7405.5	2525.8	5001.2
Crude IRR	19.24	23.5	43.16	74.38
Follow up	3.4 (1.5- 5.5)	3.5 (1.5- 5.6)	2.9 (1.3- 5.5)	2.8 (1.1- 5.1)
Crude HR (95% CI), p-value	0.82 (0.62-1.1), 0.181		0.58 (0.47-0.72), <0.001	
Adj HR (95% CI), p-value	0.81 (0.62-1.11), 0.21		0.60 (0.48-0.75), <0.001	
	eGFR<30		**ACR>30**	
Outcome events, n (%)	8 (0.8)	28 (1.5)	8 (1.1)	48 (3.2)
Person-years	3693.9	7826.8	2907.4	6200.2
Crude IRR	18.14	22.23	2.75	7.74
Follow up	3.7 (1.7- 6.0)	3.7 (1.7- 6.0)	3.5 (1.6- 5.7)	3.8 (1.6- 6.1)
Crude HR (95% CI), p-value	0.63 (0.29-1.37), 0.242		0.36 (0.17-0.76), 0.007	
Adj HR (95% CI), p-value	0.74 (0.32- 1.70), 0.48		0.36 (0.17-0.77), 0.009	
Sensitivity analysis	**Two consecutive eGFR <60**		**Two consecutive ACR≥3**	
Population, n	963	1931	924	1795
Outcome events, n (%)	67 (7.0)	174 (9.0)	46 (5.0)	168 (9.4)
Person-years	3482.7	7405.5	3419.7	6675.1
Crude IRR	19.24	23.50	13.45	25.17
Follow up	3.2 (1.5- 5.3)	3.5 (1.4- 5.6)	3.3 (1.5- 5.4)	3.3 (1.4- 5.6)
Crude HR (95% CI), p-value	0.83 (0.62- 1.09), 0.181		0.53 (0.39- 0.74), <0.001	
Adj HR (95% CI), p-value	0.83 (0.62- 1.11), 0.21		0.52 (0.37- 0.72), <0.001	

IRR= Incidence Rate/1000 person-years

Crude HR=Unadjusted Hazard Rate ratio

Adj HR= Adjusted Hazard Rate ratio; Adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration and baseline HbA1c and medications including ACE inhibitors, anti-lipid drugs and insulin.