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ARTICLE

Effect of Roux-en-Y gastric bypass surgery on diabetes remission and complications in individuals with type 2 diabetes: a Danish population-based matched cohort study

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Abstract

Aims/hypothesis The aim of this study was to examine the effect of Roux-en-Y gastric bypass (RYGB) surgery on diabetes remission, subsequent diabetes relapse and micro- and macrovascular complications in individuals with type 2 diabetes and obesity (BMI >35 kg/m^2) in a real-world setting.

Methods This was a population-based cohort study of 1111 individuals with type 2 diabetes treated by RYGB at hospitals in Northern Denmark (2006–2015), and 1074 matched non-operated individuals with type 2 diabetes. Diabetes remission was defined as no glucose-lowering drug use with HbA_{1c} <48 mmol/mol (<6.5%), or metformin monotherapy with HbA_{1c} <42 mmol/mol (<6.0%). Data on complications were ascertained from medical registries with complete follow-up.

Results At 1 year of follow-up, 74% of the cohort treated by RYGB experienced diabetes remission, while 27% had relapsed after 5 years. Predictors of non-remission were age >50 years, diabetes duration >5 years, use of glucose-lowering drugs other than metformin, and baseline HbA_{1c} >53 mmol/mol (>7.0%). Compared with the non-operated cohort using adjusted Cox regression (5.3 years follow-up), the cohort treated by RYGB had 47% lower risk of microvascular complications (HR 0.53 [95% CI 0.38, 0.73]) and a statistically non-significant 24% lower risk of macrovascular complications (HR 0.76 [95% CI 0.49, 1.18]). Diabetes remission vs non-remission at 1 year was associated with reduced HR of 0.43 (95% CI 0.25, 0.72) for microvascular complications and with HR of 0.76 (95% CI 0.40, 1.45) for macrovascular complications.

Conclusions/interpretation In routine clinical care, three out of four individuals with type 2 diabetes and obesity treated by RYGB experienced diabetes remission after 1 year, whereas 27% of these individuals had relapsed at 5 years follow-up. RYGB was associated with substantially decreased risk of microvascular complications and non-significantly fewer macrovascular complications, with early diabetes remission as a clear predictor of reduced microvascular complications.

Keywords Diabetes remission · Gastric bypass · Macrovascular complications · Microvascular complications · Population-based study · Roux-en-Y gastric bypass · Type 2 diabetes

Abbreviations

CCI	Charlson comorbidity index
CRS	Danish Civil Registration System
DNHPD	Danish National Health Service Prescription Database
DNPR	Danish National Patients Registry
GLD	Glucose-lowering drug
IQR	Interquartile range
IR	Incidence rate
IRR	Incidence rate ratio
RYGB	Roux-en-Y gastric bypass
SOS	Swedish Obese Subjects

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Introduction

Within the last 20–30 years, bariatric surgery has been introduced as a treatment for obesity with and without type 2

Research in context

What is already known about this subject?

- Roux-en-Y gastric bypass (RYGB) resolves type 2 diabetes in selected cohorts but there is a risk of diabetes relapse
- A few studies of mixed bariatric surgical procedures suggest an effect on subsequent micro- and macrovascular complications

What is the key question?

- What is the effect of RYGB surgery on diabetes remission and micro- and macrovascular complications in individuals with type 2 diabetes and BMI ≥35 kg/m^2 in a real-world setting?

What are the new findings?

- Seventy-four per cent of individuals with type 2 diabetes treated by RYGB experienced diabetes remission within 1 year, although 27% had relapsed after 5 years
- Non-remission was predicted by age >50 years, diabetes duration >5 years, use of glucose-lowering drugs other than metformin and baseline HbA_{1c} >53 mmol/mol (>7.0%)
- Relative to a matched non-operated cohort, the RYGB group had an adjusted HR of 0.53 (95% CI 0.38, 0.73) for microvascular complications and 0.76 (95% CI 0.49, 1.18) for macrovascular complications

How might this impact on clinical practice in the foreseeable future?

- Our results confirm high diabetes remission rates following RYGB in everyday clinical practice, with a positive effect on microvascular, and possibly macrovascular, complications, especially if surgery is performed early after diabetes diagnosis

diabetes [1, 2]. Until recently, Roux-en-Y gastric bypass (RYGB) was the surgical procedure of choice, especially when treating individuals with both obesity and type 2 diabetes [3]. Depending on study design and baseline participant characteristics, reported short-term resolution of type 2 diabetes following RYGB varies from 75% to 90% [4–10]. In single-centre clinical trials, younger age, lower HbA_{1c}, shorter diabetes duration, male sex and lesser severity of diabetes has predicted higher chance of diabetes remission [11, 12]. On the other hand, emerging long-term follow-up data reveal a considerable risk of type 2 diabetes relapse after initial remission [12, 13]. Whether chances of remission, relapse and predictors of remission apply to large real-world population-based cohorts with complete follow-up is unknown [14, 15].

A few long-term follow-up studies have examined the effect of mixed bariatric surgical procedures on micro- and macrovascular complications of diabetes in larger cohorts. The Swedish Obese Subjects (SOS) study reported 56% and 32% reduced risk, respectively, of microvascular and macrovascular complications in 343 participants (13% with RYGB) for 17.6 years [16]. Johnson et al reported 78% and 61% reduced risk of microvascular and macrovascular complications, respectively, in 2580 participants (percentage with RYGB not reported) during 21 months of follow-up [17]. Very recently, O'Brien et al reported a 59% reduced risk of microvascular complications in 4024 operated individuals (76% with RYGB) during 4.3 years of follow-up [18]; macrovascular complications were not investigated.

We used real-world Danish healthcare data with complete follow-up to investigate the effect of RYGB on diabetes remission, predictors of non-remission, risk of diabetes relapse, risk of surgical complications and the incidence of micro- and macrovascular complications in a type 2 diabetes cohort treated by RYGB and a matched non-operated type 2 diabetes comparison cohort.

Methods

Setting We conducted a population-based observational cohort study in individuals with type 2 diabetes living in Northern Denmark (1.8 million residents). All Danish residents are assigned an identification number in the Danish Civil Registration System (CRS) either at birth or upon immigration, which allows unambiguous individual-level linkage of registries with complete follow-up [19]. In this study, we linked data from the CRS [19], the Danish National Patients Registry (DNPR) [20], the Danish National Health Service Prescription Database (DNHPD) [21] and the LABKA database (with clinical laboratory information from both primary and secondary care), ensuring complete data coverage of the entire population [22]. The Danish National Board of Health provides the Danish population with tax-supported healthcare, including partial reimbursement of prescription drug expenses and full payment for bariatric surgery if fulfilling specific criteria (BMI >35 kg/m^2 in the case of type 2 diabetes) [23].

During the study period, bariatric surgery was performed in five hospitals in Northern Denmark. This study was approved by the Danish Data Protection Agency (2014-54-0922 KEA-2015-4). Since no patient contact was involved, no separate permission from the Danish Scientific Ethical Committee was required according to Danish Legislation.

Assembly of RYGB and comparison cohorts We first identified all individuals (age >18 years) with type 2 diabetes based on prescriptions of one or more glucose-lowering drugs (GLDs) from 1 January 2005 to 31 December 2015. To exclude individuals with likely type 1 diabetes, we excluded individuals <30 years of age at the time of filling a first prescription for insulin only. We then identified our RYGB-operated type 2 diabetes cohort as individuals registered with a procedure code for RYGB from 1 January 2006 to 31 December 2015 in the DNPR. Individuals had to be current GLD users, (within the last 180 days of the RYGB date/the index date). We excluded women with polycystic ovarian syndrome, an alternative indication for RYGB surgery (see electronic supplementary material [ESM] Table 1). Individuals with type 2 diabetes not treated by RYGB or any other bariatric surgery during the study period and who were current GLD users on the index date of an RYGB-operated individual were eligible for the matched comparison cohort. For each individual treated by RYGB, we sampled one individual without RYGB, matched with replacement on the index date, on year of birth (calendar year), sex, place of residence (regions) and calendar year of diabetes diagnosis. Algorithms on cohort formation are shown in ESM Table 1.

Baseline variables and potential confounders From the CRS and DNHPD, we retrieved information on age, sex and treated diabetes duration (time since first GLD prescription) on the index date. We also ascertained data on potential confounders associated with RYGB as choice of treatment and subsequent chance of diabetes remission or risk of diabetes complications. From the DNHPD, we assessed use of drugs, including type of GLD and blood-pressure-lowering, lipid-lowering and antithrombotic drugs (within 100 days before the index date). Micro- and macrovascular complications within 10 years prior to index date, including diabetic retinopathy, nephropathy and neuropathy, cerebrovascular disease, ischaemic heart disease and peripheral and abdominal vascular disease were assessed from the DNPR as described in detail in ESM Table 1. Likewise, we retrieved data on 19 major comorbid disease categories according to the Charlson Comorbidity index (CCI) based on the DNPR [24, 25]. We calculated the CCI score for each individual, excluding diabetes as this was the index disease in our study [26]. Using the LABKA database, we assessed baseline serum creatinine and corresponding eGFR values (within 1 year before the index date) and HbA_{1c} (within 100 days before the index date). Finally, we retrieved data on diagnosis or treatment of selected conditions not included in the CCI, as well as data on alcohol abuse from the DNHPD and the DNPR. Categorisation of all characteristics, together with detailed algorithms and codes, is shown in ESM Table 1.

Diabetes remission, non-remission and relapse For each 6 month period of follow-up, we defined diabetes remission as no use of GLD and an HbA_{1c} <48 mmol/mol (<6.5%). Because metformin therapy is often continued in Danish clinical practice even after observed diabetes remission, we also accepted an HbA_{1c} <42 mmol/mol (<6.0%) with use of metformin only as diabetes remission. If individuals were exposed to neither GLD use nor any HbA_{1c} testing during a given 6 month period, we categorised them as being in diabetes remission. Conversely, we defined non-remission as use of any GLD, except use of metformin only in combination with HbA_{1c} <42 mmol/mol (<6%), or any HbA_{1c} ≥48 mmol/mol (≥6.5%) independent of GLD use. We defined diabetes relapse as occurrence of HbA_{1c} ≥48 mmol/mol (≥6.5%) or a new prescription for a GLD after initial discontinuation [27]. The completeness of HbA_{1c} measurements is shown in ESM Table 2.

Diabetes complication outcomes Study outcomes included microvascular complications (diabetic retinopathy, diabetic neuropathy and diabetic kidney disease) and macrovascular complications (ischaemic heart disease, cerebrovascular disease and peripheral- and abdominal vascular disease) and were ascertained using all available inpatient and outpatient diagnoses recorded in the DNPR [28, 29] (ESM Table 3). In addition, we assessed changes in serum creatinine and eGFR.

Risk of surgical complications We calculated the risk of readmission with surgical complications at 30 and 90 days following RYGB, applying a previously published algorithm [30]. Details are shown in ESM Table 4.

Statistical analysis We followed all participants from the index date until death, emigration out of Northern Denmark or end of study period (31 December 2015). Loss to follow-up was not a concern because Danish registries receive complete data through mandatory reporting from the entire Danish public healthcare and administrative system. We presented baseline characteristics as medians with interquartile range (IQR) and proportions (*n* [%]). For each 6 month period after the index date, each individual was categorised as being in diabetes remission or not (i.e. prevalent remission [15], with the ability to shift category every 6 months and vice versa), with diabetes remission within the first year after the index date as primary endpoint. Next, we used modified Poisson regression to explore predictors for not achieving the diabetes remission endpoint in the RYGB cohort. Third, in the subgroup of the RYGB cohort with diabetes remission within the first year, we assessed the annual prevalence of diabetes relapse from day 366 and onwards, with our main endpoint being prevalence of relapse at

year 5. Fourth, we calculated incidence rate (IR) and incidence rate ratio (IRR) of incident micro- and macrovascular complications (hospital coded) and renal outcomes (LABKA database) and applied Cox proportional hazards regression analysis to estimate hazards of incident microvascular and macrovascular complications following the index date in the RYGB cohort vs the age-, sex- and diabetes duration-matched comparison cohort. We further adjusted in the final models for index date values of HbA_{1c}, history of microvascular complications (for macrovascular endpoint also for macrovascular history), level of CCI score, mental depression, use of blood-pressure-lowering, lipid-lowering and antithrombotic drugs and type of GLD used. Fifth, we used Cox regression to examine hazards of diabetes complications, comparing RYGB-operated individuals with and without successful diabetes remission within the first year, starting follow-up at day 366 and excluding from this analysis all RYGB-operated individuals with micro- or macrovascular complications between the index date and day 365. In this analysis, sample size allowed for adjustment for sex, age, diabetes duration and micro-and macrovascular disease before the index date. For all Cox regression models, proportional hazards assumption was fulfilled after controlling log–log plots and residuals.

Results

Characteristics of cohorts The RYGB cohort included 1111 individuals and the matched non-operated comparison cohort included 1074 individuals. The median follow-up time was 5.3 (IQR 4.0, 6.3) years in the RYGB cohort and 5.2 (IQR 3.9, 6.2) years in the comparison cohort. In the RYGB cohort, the median age was 46.8 (IQR 39.9, 54.3) years, 63.5% were women and median diabetes duration was 3.6 (IQR 1.1, 7.0) years at the index date, similar to the comparison cohort. Median HbA_{1c} at baseline (51 mmol/mol [6.8%] vs 53 mmol/mol [7.0%]) and proportion with microvascular complications were also similar, while baseline macrovascular complications and use of blood-pressure-lowering drugs were more prevalent in the RYGB cohort (Table 1).

Diabetes remission and relapse following RYGB As shown in Fig. 1, during the first 6 months of follow-up 65% of the RYGB cohort fulfilled criteria of remission, increasing to 74% at 6–12 months and surpassing 70% prevalent remission for every 6 month period in the first 5 years. The corresponding data for the comparison cohort are shown in ESM Fig. 1. Among individuals in the RYGB cohort who were in remission within the first year of follow-up, 6% (47/746), 12% (82/689), 18% (111/620) and 27% (133/492) had relapsed at 2, 3, 4 and 5 years after RYGB, respectively (ESM Fig. 2). Thus, 73% (359/492) of those in remission after the first year were still in remission 5 years after RYGB. Nevertheless, since the prevalent remission stayed above 70%, this implies that some RYGB-operated individuals who were not deemed to be in remission within the first year achieved remission later in the follow-up period. Characteristics of the RYGB cohort based on remission ($n = 786$) or non-remission ($n = 275$) status within the first year of follow-up are shown in ESM Table 5. Predictors of not achieving remission within the first year were as follows: age group 50–60 years (RR 0.88 [95% CI 0.81, 0.96]) or ≥60 years (RR 0.83 [95% CI 0.72, 0.97]) vs age group <40 years; diabetes duration 5–8 years (RR 0.87 [95% CI 0.79, 0.97]) or ≥8 years (RR 0.73 [95% CI 0.62, 0.86]) vs <2 years; HbA_{1c} ≥53 mmol/mol (≥7.0%) (RR 0.81 [95% CI 0.75, 0.88]) and use of GLDs other than metformin (RR 0.90 [95% CI 0.81, 1.00]), with insulin use being the strongest predictor of non-remission (RR 0.57 [95% CI 0.48, 0.68]) (Fig. 2). In contrast, CCI score, mental depression or other psychiatric disease did not materially affect chance of remission.

Microvascular and macrovascular complications after RYGB During follow-up, the IRs for any microvascular event were 21.5/1000 person-years among RYGB-operated individuals and 38.7/1000 person-years among the comparison group (IRR 0.56 [0.44, 0.70]). Diabetic retinopathy occurred in 13.9/1000 person-years of RYGB-operated individuals vs 27.6/1000 person-years of comparisons (IRR 0.52 [0.39, 0.69]). Hospital-coded diabetic kidney disease occurred in 3.6/1000 person-years of RYGB-operated individuals vs 6.6/1000 person-years of comparisons (IRR 0.54 (0.31, 0.94). Diabetic neuropathy occurred in 5.1/1000 of RYGB-operated individuals vs 6.1/1000 of comparisons (IRR 0.84 [0.50, 1.39]). Cumulative incidence curves for any microvascular event (diabetic kidney disease, retinopathy and neuropathy, whichever came first) in the two cohorts are presented in Fig. 3a and showed a higher cumulative incidence in the comparison cohort. Changes in creatinine and eGFR are displayed in ESM Figs 3, 4 and ESM Tables 6, 7. Relative to the comparison cohort, the crude HR for microvascular complications in the RYGB cohort was 0.54 (95% CI 0.42, 0.70). After adjustment for potential confounders, the RYGB cohort had a 47% lower hazard of incident microvascular disease vs the comparison cohort (HR 0.53 [95% CI 0.38, 0.73]) after a median follow-up of 5.3 (IQR 4.0, 6.3) years.

IRs for any macrovascular event were 11.7/1000 person-years among RYGB-operated individuals and 15.0/1000 person-years among individuals in the comparison group (IRR 0.78 [0.56, 1.09]). Ischaemic heart disease occurred in 2.9/1000 person-years among RYGB-operated individuals vs 5.3/1000 person-years among comparisons (IRR 0.54 [0.29, 1.00]). In contrast, cerebrovascular disease occurred in 4.1/1000 person-years among RYGB-operated individuals vs 3.2/1000 person-years among comparisons (IRR 1.29 [0.69, 2.41]). Peripheral- and abdominal vascular disease occurred in 5.9/1000 person-years of RYGB-operated individuals vs 5.3/

Table 1 Index date characteristics of the RYGB and comparison cohorts with type 2 diabetes

Characteristic	RYGB cohort ($n = 1111$)	Comparison cohort ($n = 1074$)
Age, years	46.8 (39.9–54.3)	47.1 (40.4–54.3)
HbA_{1c}, mmol/mol	51 (43–60)	53 (45–66)
HbA_{1c}, %	6.8 (6.1–7.6)	7.0 (6.3–8.2)
Follow-up time, years	5.3 (4.0–6.3)	5.2 (3.9–6.2)
Diabetes duration at index date, years	3.6 (1.1–7.0)	3.5 (1.2–6.8)
Female sex, *n* (%)	706 (63.5)	681 (63.4)
Any hospital-recorded microvascular complication, *n* (%)	139 (12.5)	141 (13.1)
Diabetic retinopathy, *n* (%)	93 (8.4)	113 (10.5)
Diabetic neuropathy, *n* (%)	40 (3.6)	27 (2.5)
Diabetic kidney disease, *n* (%)	23 (2.1)	25 (2.3)
eGFR <90 ml min^{-1} [1.73 m]$^{-2}$, *n* (%)	467 (42.3)[a]	300 (36.3)[b]
eGFR <60 ml min^{-1} [1.73 m]$^{-2}$, *n* (%)	67 (6.2)[a]	35 (3.9)[b]
Serum creatinine, μmol/l	66 (57–76)	63 (55–73)
Any hospital-recorded macrovascular complication, *n* (%)	157 (14.1)	119 (11.1)
Ischaemic heart disease, *n* (%)	112 (10.1)	91 (8.5)
Cerebrovascular disease, *n* (%)	16 (1.4)	27 (2.5)
Abdominal or peripheral vascular disease, *n* (%)	47 (4.2)	28 (2.6)
Metformin only, *n* (%)	466 (41.9)	472 (43.9)
Metformin plus other oral GLDs, *n* (%)	246 (22.1)	210 (19.6)
Metformin plus insulin, *n* (%)	203 (18.3)	90 (8.4)
GLP-1 analogue, *n* (%)	9 (0.8)	6 (0.6)
Insulin only, *n* (%)	47 (4.3)	172 (16.0)
Other GLDs and insulin, *n* (%)	26 (2.3)	18 (1.7)
ACE inhibitor/ARB, *n* (%)	244 (22.0)	208 (19.4)
Any blood-pressure-lowering drug, *n* (%)	745 (67.1)	532 (49.5)
Aspirin, *n* (%)	193 (17.4)	165 (15.4)
Any antithrombotic drug, *n* (%)	229 (20.6)	197 (18.3)
Statins, *n* (%)	458 (41.2)	459 (42.7)
Any lipid-lowering drug, *n* (%)	486 (43.7)	480 (44.7)
CCI score 0, *n* (%)	912 (82.1)	889 (82.8)
CCI score 1, *n* (%)	154 (13.9)	112 (10.4)
CCI score 2, *n* (%)	38 (3.4)	48 (4.5)
CCI score ≥3, *n* (%)	7 (0.6)	25 (2.3)
Mental depression, *n* (%)	463 (41.7)	359 (33.4)
Other psychiatric disease, *n* (%)	132 (11.9)	123 (11.5)
Chronic pulmonary disease, *n* (%)	90 (8.1)	52 (4.8)
Musculoskeletal disease, *n* (%)	296 (26.6)	213 (19.8)
Alcohol abuse, *n* (%)	58 (5.2)	66 (6.1)

Data are median (IQR) or *n* (%)

The RYGB and comparison cohorts with type 2 diabetes were matched on age, sex, place of residence, calendar year of diabetes debut and diabetes duration. For detailed algorithm, see ESM Table 1

[a] $n = 1081$ in the RYGB-operated group had available baseline eGFR/creatinine data

[b] $n = 893$ in the comparison cohort had available baseline eGFR/creatinine data

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; GLP-1, glucagon like peptide-1

1000 person-years among comparisons (IRR 0.75 [0.47, 1.18]). Relative to the comparison cohort, the crude HR for any macrovascular event was 0.83 (95% CI 0.59, 1.17) (Fig. 3b), with an adjusted HR of 0.76 (95% CI 0.49, 1.18).

When examining hazards of diabetes complications, comparing RYGB-operated individuals with and without achieved diabetes remission within the first year, microvascular events were 57% lower in those with remission (HR 0.43 [95% CI

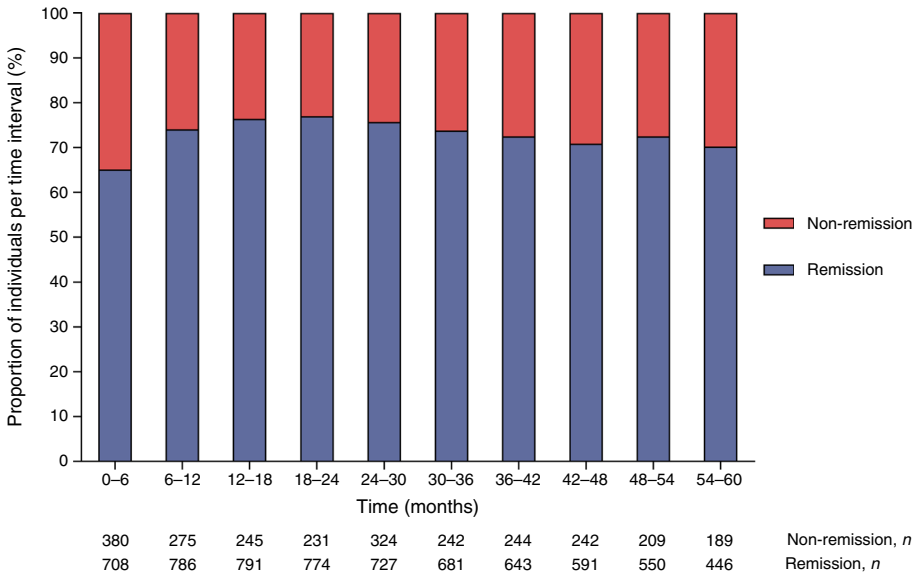

Fig. 1 Proportion of RYGB-operated individuals with diabetes remission (blue) and non-remission (red) assessed every 6 months during the first 5 years of follow-up. Each individual had the ability to shift from remission to non-remission status and vice versa every 6 months during follow-up (i.e. prevalent remission was investigated [15]). The rather constant proportion of RYGB-operated individuals observed as being in diabetes remission in each 6 month time interval during follow-up, despite successive diabetes relapses occurring, indicates that diabetes remission status following RYGB is dynamic. At each time point, diabetes remission was defined as either no use of GLDs and an HbA_{1c} <48 mmol/mol (<6.5%) or use of metformin only and an HbA_{1c} <42 mmol/mol (<6.0%). We defined non-remission as use of any GLD, except use of metformin only in combination with HbA_{1c} <42 mmol/mol (<6.0%), or any HbA_{1c} ≥48 mmol/mol (≥6.5%) independent of GLD use

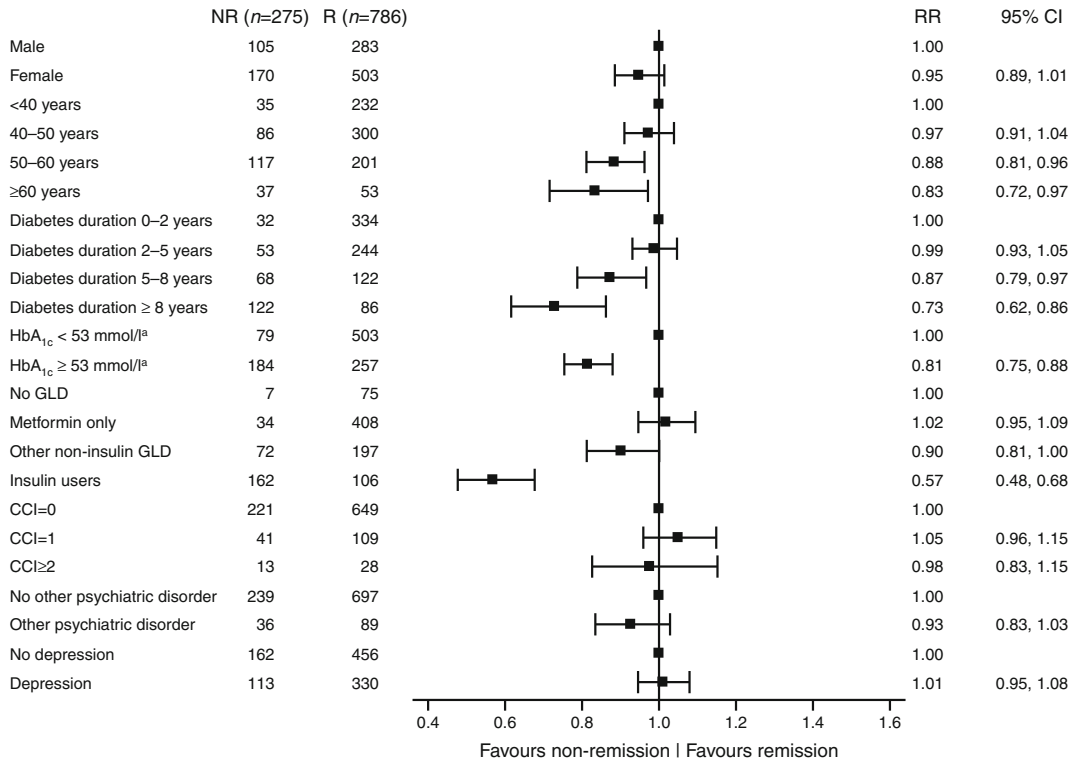

Fig. 2 Baseline predictors of lack of diabetes remission within 1 year after RYGB. Diabetes remission was defined as either no use of GLDs and an HbA_{1c} <48 mmol/mol (<6.5%) or use of metformin only and an HbA_{1c}< 42 mmol/mol (<6.0%). We defined non-remission as use of any GLD, except use of metformin only in combination with HbA_{1c} <42 mmol/mol (<6.0%), or any HbA_{1c} ≥48 mmol/mol (≥6.5%) independent of GLD use. 'Other psychiatric disorder' covers bipolar disorders, schizophrenia and severe personality disorders. [a]For HbA_{1c}, 3.6% (38/1061) had missing baseline measurements. NR, non-remission; R, remission

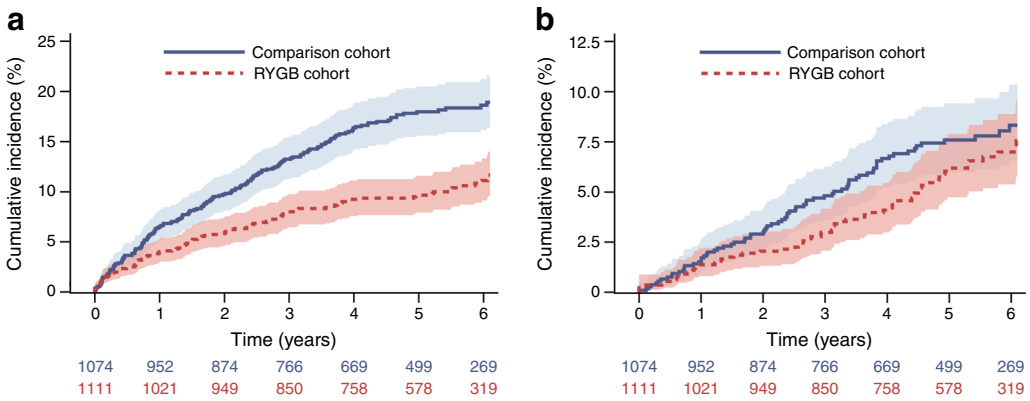

Fig. 3 Cumulative incidence of micro- and macrovascular complications in the RYGB and comparison cohorts. Microvascular complications (**a**) and macrovascular complications (**b**) in the RYGB cohort and the comparison cohort are shown with 95% CIs (shaded area). The numbers below the *x*-axis represent the number of individuals in the RYGB cohort (red) and the comparison cohort (blue) for each year of follow-up. Microvascular complications: diabetic retinopathy, diabetic neuropathy and diabetic kidney disease. Macrovascular complications: ischaemic heart disease, cerebrovascular disease and peripheral- and abdominal vascular disease. Specific diagnosis coding is given in ESM Table 3

0.25, 0.72]). The adjusted hazard of macrovascular events was 24% lower (HR 0.76 [95% CI 0.40, 1.45]).

Surgical complications During the first 30 days following RYGB, the risk of readmission due to any surgical complication was 7.5% (84/1109) (ESM Table 8). The 90-day mortality following RYGB was <0.5%.

Discussion

In this population-based real-world study with complete follow-up for median 5.3 years, 74% of individuals with type 2 diabetes treated by RYGB experienced diabetes remission after one year. There was a lower chance of remission with older age, increased diabetes duration and greater severity of diabetes at index date. Twenty-seven per cent of those in remission at 1 year experienced relapse after 5 years. Of importance to patients and healthcare providers, those who underwent RYGB surgery had substantially decreased risk of subsequent microvascular complications and a (not statistically significant) decreased risk of subsequent macrovascular complications as compared with non-operated individuals with type 2 diabetes; successful diabetes remission at 1 year was a clear predictor of fewer microvascular complications. The 30 day risk of readmission due to surgical complications after RYGB was 7.5%, higher than we previously reported among RYGB-operated individuals overall (3.3%) [30], most likely because type 2 diabetes per se disposes to surgical complications. Surgical short-term mortality was very low (<0.5%).

As Isaman et al have stressed, diabetes remission rates following RYGB reported in the literature vary substantially (25–83%) depending on definition of remission, study duration, choice of statistical analysis, whether or not attrition rates are taken into account and whether the setting is population or clinic based, hampering generalisability of previous results [15]. We deviated from the usual definition of diabetes remission [27] by counting an individual with HbA_{1c} <42 mmol/mol (<6.0%) and use of metformin only as being in diabetes remission, a definition applied in some RYGB outcome studies previously [31]. Building on the cardioprotective results of metformin observed in the UK Prospective Diabetes Study (UKPDS) [32], it is clinical practice in Denmark to continue metformin despite observed diabetes remission [30]. This more liberal definition explains the higher remission rates seen in our comparison cohort compared with those reported in previous studies (13–20% vs 0–16%) [12, 13, 16]. On the other hand, we defined type 2 diabetes in our study by use of GLD and not by specific diagnostic criteria. By excluding at baseline RYGB-operated individuals with non-pharmacologically treated type 2 diabetes, which may more likely remit following RYGB, our rates of remission might be lower than those reported in previous studies. Still, our real-world data are largely consistent with previous non-population-based single-centre observations of high 1 year diabetes remission rates [5, 7, 8, 10, 31] and 5 year relapse rates of approximately 30–50% [9, 12, 13]. Most interestingly, our findings of older age, higher HbA_{1c}, longer diabetes duration and pre-operative insulin treatment being associated with lack of remission following RYGB corroborate data from previous cohort studies [9] and single-centre randomised trials [12]. It seems these remission predictors are consistently observed independently of study type and could be included in a remission scoring system [11, 33]. Overall, our findings add evidence to the importance of regular check-ups following RYGB, despite initial diabetes remission, and also suggest that timing of RYGB is important (i.e. consider RYGB while there are still functional pancreatic beta cells). Interestingly, but without any obvious explanation, we found a trend towards male sex being a positive predictor for diabetes remission; this was also reported by Arterburn et al [9]. Our 5 year prevalent remission rate of 70% concurs with previous findings [5, 34]. Of note, there is evidence that operated individuals not reaching the threshold for diabetes remission (whatever the definition) still display better glycaemic control than non-operated individuals,

with less use of GLDs than preoperatively [12, 13, 34]. This aligns with the theory of 'metabolic memory' introduced by Coleman et al [35], suggesting that time spent in diabetes remission following RYGB is not spent in vain when it comes to reducing the risk of subsequent microvascular complications.

An important strength of our study is the inclusion of individuals with type 2 diabetes treated by a single type of bariatric surgery. Furthermore, we present real-world clinical data in a population-based setting, representing 30% of the Danish population. Our data catchment area covers both urban and rural areas, all socioeconomic groups, and all types of hospitals/clinics. Because the Danish healthcare system is state-funded, the individual economy of each patient plays no role in whether or not RYGB is offered. This setting may reduce the selection bias arising from whether or not treatment is chosen, a bias that likely affects every non-randomised study on the effects of RYGB. Our setting also ensures complete follow-up through universally covering registries [15], in contrast to clinic-based settings where patient attrition may be correlated to treatment failure [36]. Our relatively long follow-up of 5.3 years for micro- and macrovascular events is to our knowledge only surpassed by the SOS study group to date [16]. In contrast to the SOS study, which included all types of bariatric procedures, we did not depend on self-reported outcomes. Regarding diabetes remission, Adams et al presented an even longer follow-up, although that study was based on 88 participants with type 2 diabetes only [34].

A main limitation of our study was the lack in our registries of individual-level data on BMI, a factor associated with risk of type 2 diabetes and macrovascular complications [37]. In a previous study ($N = 1429$), BMI in Danish individuals treated by RYGB was 46 kg/m^2 at time of surgery and 30 kg/m^2 at 4.5 years after surgery [36]. In comparison, the average BMI of a Danish person with type 2 diabetes is approximately 30 kg/m^2 [38]. This clearly indicates that our RYGB cohort had a considerably higher BMI than the comparison cohort at baseline, also corroborated by their higher baseline prevalence of cardiovascular disease and usage of blood-pressure-lowering drugs. Any uncontrolled confounding from BMI would therefore likely have led us to underestimate the protective effect of RYGB on diabetes complications, not changing our conclusions. We also lacked data on tobacco use, which may be lower in individuals with high BMI [39] and thus might have driven the cardiovascular risk estimate in the opposite direction [37]. However, we were able to include data on chronic obstructive pulmonary disease in our analysis; this is a strong marker of smoking and was in fact over-represented in the RYGB cohort. In addition, we do not have full data coverage on HbA_{1c} in every 6 month follow-up period (although better than previous studies of RYGB [40]), which might limit the interpretation of remission and relapse. Finally, due to a limited number of the individual micro- and macrovascular complications, related both to study size and to the incomplete assessment of changes in for example retinopathy and albuminuria in registries, we lacked statistical power and were unable to calculate adjusted HRs for individual microvascular and macrovascular complications (alternatively, IRRs were reported).

Despite these limitations, our finding of a 47% lower risk of incident microvascular complications (HR 0.53 [95% CI 0.38, 0.73]) following RYGB confirms data from the few previous existing studies. The SOS study reported a 66% reduced risk (HR 0.44 [95% CI 0.34, 0.56]) of microvascular complications in a study of 343 bariatric-operated and 260 non-operated individuals with type 2 diabetes with a median follow-up of 17.6 years [16]. Johnson et al reported a 78% lower risk (HR 0.22 [95% CI 0.09, 0.49]) of microvascular complications when examining 2580 bariatric-operated individuals and 13,371 control individuals, providing 21 months of follow-up in their observational study based on insurance claims [17]. Neither of these outcome studies controlled for diabetes duration or severity markers as we did. Our findings for microvascular complications also corroborate those of a new study by O'Brien et al, reporting an adjusted HR 0.41 [95% CI 0.34, 0.48]) for microvascular complications during a median of 4.3 years follow-up in 4024 individuals treated by bariatric surgery compared with a control group [18]. Data in this study originated from four healthcare databases in the USA; although there was a disenrolment rate of more than 25% in the surgical cohort during follow-up, the study had the strength of also being able to match for baseline BMI. O'Brien et al [18] found lower risks of diabetic kidney disease, diabetic retinopathy and diabetic neuropathy in the RYGB-operated cohort, while we observed the strongest associations for reduced kidney disease and retinopathy as the main drivers of reduced microvascular complications. Our findings of improved eGFR in the RYGB cohort during the first 5 years of follow-up may be partly due to the RYGB-induced weight and muscle losses and thus not only be reflective of improved renal function. Still, although RYGB may be associated with kidney disease [41], the overall effect on kidney function appears beneficial, supported by findings on reductions in albuminuria and lower incidence of end-stage renal disease found in other studies [42, 43]. Finally, our finding that among individuals that had undergone RYGB, diabetes remission after 1 year conferred a 57% lower risk of microvascular complications (HR 0.43 [95% CI 0.25, 0.72]) additionally supports treatment by RYGB in the early years of type 2 diabetes, where chance for remission is greater.

When it comes to the effect of RYGB on macrovascular events, the magnitude of reduced risk (HR 0.76 [95% CI 0.49, 1.18]) that we observed during 5.3 years of follow-up—though statistically imprecise—aligns well with results of the observational SOS study reporting 32% reduced risk (HR 0.68 [95% CI 0.54, 0.85]) [16] and was lower than the 61% (HR 0.39 [95% CI 0.29, 0.51]) reduced risk reported by Johnson et al [17]. Again, our ability to adjust for diabetes duration and severity might partly explain the differences in estimates. We observed the strongest association for reduced ischaemic heart disease as the main driver of reduced macrovascular complications, corroborating findings from Eliasson et al [44] reporting reduced HR of fatal

and non-fatal myocardial infarction (HR 0.51 [0.21, 0.91]) in individuals with type 2 diabetes treated by RYGB.

In conclusion, the findings from this study add to the growing body of evidence on effects of bariatric surgery, specifying that RYGB does remit type 2 diabetes and is associated with a reduced risk of microvascular, and possibly macrovascular, complications, also in population-based non-selected cohorts and especially if introducing surgery at an early stage of disease. Predictors of remission success seem to be very consistent in randomised controlled trials, studies of selected cohorts and population-based studies. On the other hand, there is a substantial risk of relapsing into type 2 diabetes, which should be accounted for when advising patients and planning post-surgery care.

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Data availability All data used in the study can be obtained by applying to Statistics Denmark.

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Contribution statement LRM designed the study, researched the data and drafted the manuscript. LMB designed the study and performed the statistical analysis. BR and RWT designed the study and revised the manuscript critically. All authors contributed to the discussion and approved the final manuscript. LRM is the guarantor for the content of this article.

References

1. Davies MJ, D Alessio DA, Fradkin J et al (2018) Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 41(12):2669–2701. https://doi.org/10.2337/dci18-0033
2. Cummings DE, Rubino F (2018) Metabolic surgery for the treatment of type 2 diabetes in obese individuals. Diabetologia 61(2): 257–264. https://doi.org/10.1007/s00125-017-4513-y
3. Angrisani L, Santonicola A, Iovino P et al (2017) Bariatric surgery and endoluminal procedures: IFSO worldwide survey 2014. Obes Surg 27(9):2279–2289. https://doi.org/10.1007/s11695-017-2666-x
4. Courcoulas AP, Belle SH, Neiberg RH et al (2015) Three-year outcomes of bariatric surgery vs lifestyle intervention for type 2 diabetes mellitus treatment: a randomized clinical trial. JAMA Surg 150(10): 931–940. https://doi.org/10.1001/jamasurg.2015.1534
5. Courcoulas AP, King WC, Belle SH et al (2018) Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study. JAMA Surg 153(5):427–434. https://doi.org/10.1001/jamasurg.2017.5025
6. Ikramuddin S, Billington CJ, Lee WJ et al (2015) Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomised, controlled trial. Lancet Diabetes Endocrinol 3(6):413–422. https://doi.org/10.1016/S2213-8587(15)00089-3
7. Cummings DE, Arterburn DE, Westbrook EO et al (2016) Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial. Diabetologia 59(5):945–953. https://doi.org/10.1007/s00125-016-3903-x
8. Halperin F, Ding SA, Simonson DC et al (2014) Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA Surg 149(7):716–726. https://doi.org/10.1001/jamasurg.2014.514
9. Arterburn DE, Bogart A, Sherwood NE et al (2013) A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg 23(1):93–102. https://doi.org/10.1007/s11695-012-0802-1
10. Yip S, Plank LD, Murphy R (2013) Gastric bypass and sleeve gastrectomy for type 2 diabetes: a systematic review and meta-analysis of outcomes. Obes Surg 23(12):1994–2003. https://doi.org/10.1007/s11695-013-1030-z
11. Still CD, Wood GC, Benotti P et al (2014) Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. Lancet Diabetes Endocrinol 2(1): 38–45. https://doi.org/10.1016/S2213-8587(13)70070-6
12. Schauer PR, Bhatt DL, Kirwan JP et al (2017) Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 376(7):641–651. https://doi.org/10.1056/NEJMoa1600869
13. Mingrone G, Panunzi S, De Gaetano A et al (2015) Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 386(9997):964–973. https://doi.org/10.1016/S0140-6736(15)00075-6
14. Wolfe BM, Belle SH (2014) Long-term risks and benefits of bariatric surgery: a research challenge. JAMA 312(17):1792–1793. https://doi.org/10.1001/jama.2014.12966
15. Isaman DJM, Rothberg AE, Herman WH (2018) The effect of attrition on reported diabetes remission rates following Roux-en-Y gastric bypass: a sensitivity analysis. Obes Surg 28(5):1308–1312. https://doi.org/10.1007/s11695-017-2995-9
16. Sjostrom L, Peltonen M, Jacobson P et al (2014) Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 311(22):2297–2304. https://doi.org/10.1001/jama.2014.5988
17. Johnson BL, Blackhurst DW, Latham BB et al (2013) Bariatric surgery is associated with a reduction in major macrovascular and microvascular complications in moderately to severely obese patients with type 2 diabetes mellitus. J Am Coll Surg 216(4):545–556; discussion 556-558. https://doi.org/10.1016/j.jamcollsurg.2012.12.019
18. O'Brien R, Johnson E, Haneuse S et al (2018) Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. Ann Intern Med 169(5):300–310. https://doi.org/10.7326/M17-2383
19. Schmidt M, Pedersen L, Sorensen HT (2014) The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 29(8):541–549. https://doi.org/10.1007/s10654-014-9930-3

20. Lynge E, Sandegaard JL, Rebolj M (2011) The Danish National Patient Register. Scand J Public Health 39(7_suppl):30–33. https://doi.org/10.1177/1403494811401482
21. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sorensen HT (2012) Existing data sources for clinical epidemiology: the Danish National Database of Reimbursed Prescriptions. Clin Epidemiol 4:303–313. https://doi.org/10.2147/CLEP.S37587
22. Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW (2011) Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol 3:133–138. https://doi.org/10.2147/CLEP.S17901
23. Sundhedsstyrelsen D (2008) Forløbsprogram for diabetes. Available from: https://www.sst.dk/~/media/5C35B9DEA91B4E0A91458076F1994019.ashx, accessed 7 Jun 2017
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383. https://doi.org/10.1016/0021-9681(87)90171-8
25. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT (2011) The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 11(1):83. https://doi.org/10.1186/1471-2288-11-83
26. Thomsen RW, Baggesen LM, Svensson E et al (2015) Early glycaemic control among patients with type 2 diabetes and initial glucose-lowering treatment: a 13-year population-based cohort study. Diabetes Obes Metab 17(8):771–780. https://doi.org/10.1111/dom.12484
27. Buse JB, Caprio S, Cefalu WT et al (2009) How do we define cure of diabetes? Diabetes Care 32(11):2133–2135. https://doi.org/10.2337/dc09-9036
28. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M (2003) The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol 56(2):124–130. https://doi.org/10.1016/S0895-4356(02)00591-7
29. Wildenschild C, Mehnert F, Thomsen RW et al (2013) Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. Clin Epidemiol 6:27–36
30. Gribsholt SB, Svensson E, Richelsen B, Raundahl U, Sorensen HT, Thomsen RW (2018) Rate of acute hospital admissions before and after Roux-en-Y gastric bypass surgery: a population-based cohort study. Ann Surg 267(2):319–325. https://doi.org/10.1097/SLA.0000000000002113
31. Dicker D, Yahalom R, Comaneshter DS, Vinker S (2016) Long-term outcomes of three types of bariatric surgery on obesity and type 2 diabetes control and remission. Obes Surg 26(8):1814–1820. https://doi.org/10.1007/s11695-015-2025-8
32. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854–865
33. Debedat J, Sokolovska N, Coupaye M et al (2018) Long-term relapse of type 2 diabetes after Roux-en-Y gastric bypass: prediction and clinical relevance. Diabetes Care 41(10):2086–2095. https://doi.org/10.2337/dc18-0567
34. Adams TD, Davidson LE, Litwin SE et al (2017) Weight and metabolic outcomes 12 years after gastric bypass. N Engl J Med 377(12):1143–1155. https://doi.org/10.1056/NEJMoa1700459
35. Coleman KJ, Haneuse S, Johnson E et al (2016) Long-term microvascular disease outcomes in patients with type 2 diabetes after bariatric surgery: evidence for the legacy effect of surgery. Diabetes Care 39(8):1400–1407. https://doi.org/10.2337/dc16-0194
36. Harper J, Madan AK, Ternovits CA, Tichansky DS (2007) What happens to patients who do not follow-up after bariatric surgery? Am Surg 73:181–184
37. Grundy SM, Benjamin IJ, Burke GL et al (1999) Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 100(10):1134–1146. https://doi.org/10.1161/01.CIR.100.10.1134
38. Christensen DH, Nicolaisen SK, Berencsi K et al (2018) Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project cohort of newly diagnosed patients with type 2 diabetes: a cohort profile. BMJ Open 8(4):e017273. https://doi.org/10.1136/bmjopen-2017-017273
39. Gribsholt SB, Pedersen L, Richelsen B, Dekkers O, Thomsen RW (2018) Body mass index of 92,027 patients acutely admitted to general hospitals in Denmark: associated clinical characteristics and 30-day mortality. PLoS One 13(4):e0195853. https://doi.org/10.1371/journal.pone.0195853
40. Yska JP, van Roon EN, de Boer A, et al (2015) Remission of type 2 diabetes mellitus in patients after different types of bariatric surgery: a population-based cohort study in the United Kingdom. JAMA Surg 150(12):1126–1133
41. Upala S, Jaruvongvanich V, Sanguankeo A (2016) Risk of nephrolithiasis, hyperoxaluria, and calcium oxalate supersaturation increased after Roux-en-Y gastric bypass surgery: a systematic review and meta-analysis. Surg Obes Relat Dis 12(8):1513–1521. https://doi.org/10.1016/j.soard.2016.04.004
42. Carlsson LM, Peltonen M, Ahlin S et al (2012) Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. N Engl J Med 367(8):695–704. https://doi.org/10.1056/NEJMoa1112082
43. Shulman A, Peltonen M, Sjostrom CD et al (2018) Incidence of end-stage renal disease following bariatric surgery in the Swedish Obese Subjects Study. Int J Obes 42(5):964–973. https://doi.org/10.1038/s41366-018-0045-x
44. Eliasson B, Liakopoulos V, Franzen S et al (2015) Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nationwide, matched, observational cohort study. Lancet Diabetes Endocrinol 3(11):847–854. https://doi.org/10.1016/S2213-8587(15)00334-4