Title: Effects of bariatric surgery on kidney diseases, cardiovascular diseases, mortality and severe hypoglycaemia among patients with type 2 diabetes mellitus

Short running title: Bariatric surgery reduced mortality and CVD

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Abstract

Background: Bariatric surgery has been widely indicated for the management of obesity and related comorbidities. However, there are uncertainties on the risks of post-bariatric severe hypoglycaemia (SH), cardiovascular diseases (CVD), end-stage renal diseases (ESRD) and all-cause mortality in obese patients with type 2 diabetes mellitus (T2DM), especially among Asian population.

Methods: A retrospective population-based cohort of 1,690 obese T2DM patients who were free of CVD and ESRD were assembled based on 2006-2017 Hospital Authority database. One-to-five propensity-score matching was used to balance baseline covariates between patients in bariatric surgery and control groups. Incidence rates (IR) of SH, CVD, stage 4/5 chronic renal diseases, ESRD and all-cause mortality events for two groups were calculated. Hazard ratios (HR) for SH, CVD, and stage 4/5 chronic renal diseases events were assessed using Cox proportional hazard models. Changes in estimated glomerular filtration rate (eGFR), and urine albumin-creatinine ratio (UACR) were measured up to 60 months.

Results: Over a mean follow-up period of 32 months with 5725 person-years, cumulative incidences of mortality, CVD, stage 4/5 chronic kidney diseases, ESKD and SH were 0, 0.036, 0.050, 0.017, and 0.020, respectively. Surgery group had a significant reduction in risk of CVD events (HR=0.464, P=0.015), and no occurrence of mortality events. However, there were no significant differences in risks of SH (HR=0.0.469, 95% Confidence Interval [CI]=0.204-1.081), stage 4/5 chronic kidney diseases (HR=0.896, 95% CI=0.519-1.545) and ESKD (HR=0.666, 95% CI=0.264-1.683) between two groups, although IRs were lower in the surgery group. Surgical patients had significantly higher eGFR within 12 months, and had significantly lower UACR until 48 months.

Conclusions: Among obese T2DM patients, bariatric surgery lowered the risk of CVD and mortality, and was beneficial towards the kidney outcomes.

Key words: Bariatric surgery, ESKD, Cardiovascular, Severe hypoglycaemia, Type 2 diabetes

Key Leaning Points

What is already known about this subject?

- The prevalence of obesity is on the rise and it is now a global epidemic with many facing a huge disease burden. Obesity is associated with increased morbidity and mortality from multiple co-morbidities such as type 2 diabetes mellitus (T2DM) and both diseases have emerged as enormous public health problems
- Bariatric surgery, a widely indicated intervention for the management of obesity, is associated with reduced risks of mortality and has cardiovascular protective and renal protective effects among Caucasian populations with obesity.
- There are still uncertainties on the risks of post-bariatric severe hypoglycaemia (SH), cardiovascular diseases (CVD), end-stage kidney diseases (ESKD) and all-cause mortality in obese patients with type 2 diabetes mellitus, especially among Asian population.

What this study adds?

- Surgery group had a significant reduction in risk of CVD events (HR=0.464, P=0.015), and no occurrence of mortality events.
- There were no significant differences in risks of SH (HR=0.0.469, 95% CI=0.204-1.081), stage 4/5 chronic kidney diseases (HR=0.896, 95% CI=0.519-1.545) and ESKD (HR=0.666, 95% CI=0.264-1.683) between two groups, although IRs were lower in the surgery group.
- Surgical patients had significantly higher estimated glomerular filtration rate within 12 months, and had significantly lower urine albumin-creatinine ratio until 48 months.

What impact this may have on practice or policy?

- Findings of this study addressed the research gap in enhancing our knowledge in understanding the benefits of bariatric surgery, as providing an effective mean of disease management and addressing the increasing disease burden of patients with co-existence of obesity and T2DM.

Introduction

The prevalence of obesity is on the rise and it is now a global epidemic with many facing a huge disease burden [1]. Obesity is associated with increased morbidity and mortality from multiple co-morbidities such as type 2 diabetes mellitus (T2DM) and both diseases have emerged as enormous public health problems [2, 3]. Nowadays, nighty percent of individuals with type 2 diabetes aged 16-54 years are overweight or obese in England [4].
The relationship between obesity and diabetes is of such interdependence, in which complex interactions exist [5, 6].

Formulating the most appropriate strategy for patients with obesity requires consideration on various factors. Interventional therapy with bariatric surgery is indicated for patients with obesity who have been unresponsive to lifestyle intervention with sufficient weight loss in achieving targeted health outcome as stated by the American College of Cardiology (ACC) and the American Heart Association (AHA) [7]. In addition, the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) recognized the vital role of bariatric surgery as part of the standard treatment for obese diabetic patients [8, 9]. Standard bariatric procedures at present include adjustable gastric banding (AGB), laparoscopic sleeve gastrectomy (SG) and laparoscopic Roux-en-Y gastric bypass (RYGB), in which SG and RYGB are more commonly performed nowadays [10].

In recent years, there has been an increasing interest in examining the cardiovascular protective effect of bariatric surgery. Investigations in the past revealed the mechanisms in which the cardiovascular protective effects are exerted, through a reduction in inflammation and thrombosis, restoration of favourable adipokine secretory profile, improvement in endothelial function, reduction in cardiovascular risk factors, restoration of normal metabolism and improvement in cardiac structure and function [6, 11].

According to a systematic review and meta-analysis, bariatric surgery was not only associated with a significantly reduced risk of composite cardiovascular adverse events, but also associated with significant reduction in specific endpoints of myocardial infarction and stroke [11]. Previous Swedish Obese Study (SOS) demonstrated that bariatric surgery resulted in a significant reduction of the risks of overall mortality, CVD events such as myocardial infarction (MI) and stroke [12-14]. Among a large cohort in Israel, those who

underwent bariatric surgery had statistically significant lower rates of all-cause mortality over 11 years of follow-up compared to other non-surgical patients [15]. Bariatric surgery resulted in reduced incidence in CVD complications after a median follow-up of 18 years [16]. The duration of existing diabetes, instead of the baseline BMI, had a positive influence on the likelihood of CVD complications [16, 17]. An Italian longitudinal study over a 23-year period demonstrated preventive effect of gastric banding on mortality [18]. A recent study in the US compared risks of major composite CVD events between RYGB patients and non-surgical group over a follow up period up to 12 years after surgery. Results revealed a statistically significant reduction in their risks with RYGB. The risk of severe cardiovascular events (composite of MI, stroke and congestive heart failure) almost halved 8 years after surgery compared to those without the operation with most cardio-protective effect demonstrated for congestive heart failure followed by MI and stroke [6]. The cardiovascular beneficial effects of bariatric surgery were also assessed over among Chinese population across a year of follow-up using the United Kingdom Prospective Diabetes Study (UKPDS) risk engine for calculation. One of the main findings from the assessment was that there was a significant reduction in predicted 10-year Coronary Heart Disease (CHD) and fatal CHD risk up to 50% following the operation. Results were yet insignificant for risk reduction for stroke [19].

Bariatric surgery is also associated with long-term improvement of kidney function [19-22], due to its effective management of risk factors for chronic kidney diseases, such as obesity and T2DM [23]. Findings of a propensity score-matched cohort study in US showed that bariatric surgery was associated with a 58% lower risk of eGFR decline of ≥30% and a 57% lower risk of doubling of serum creatinine or ESKD [20, 21]. The landmark study, SOS, with a median follow-up of 18 years, confirmed the long-term protective kidney effect of bariatric surgery in obese patients, with results showing that patients with bariatric surgery had significantly lower incidence rates (IRs) of end-stage kidney diseases (ESKD) alone and in combination with chronic kidney disease stage 4 than those without bariatric surgery [22].

Despite bariatric surgery reduces the risk of CVD and slows the progression to ESKD, severe hypoglycemia (SH) remains a rare, yet concerning event after bariatric surgery, particularly gastric bypass [24, 25]. A nationwide cohort study with 5,040 bariatric surgery patients found that only 0.2% of patients were found hypoglycemia following gastric bypass [25]. However,

SH after bariatric surgery can be extremely dangerous, as the symptoms could last for months to years and may present with neuroglycopenia [26].

The aim of this study is to assess risks of post-bariatric hypoglycaemia, CVD, ESKD and all-cause mortality in obese patients with T2DM.

Materials and Methods

Data Source and Study Population

We assembled the population-based retrospective cohort from the Hospital Authority administrative database in the Hong Kong adult diabetes mellitus population from January 1, 2006 to December 31, 2017. Hospital Authority database has been extensively used for conducting population-based cohort studies for diabetes mellitus [27-29]. Documented T2DM diagnosis was defined according to the International Classification of Primary Care, Version 2 (ICPC-2) code or International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Clinical Modification (ICD-9-CM) codes.

In this cohort, 664 diabetes patients with obesity who underwent laparoscopic sleeve gastrectomy (ICD-9-CM procedure code of 43.89), laparoscopic gastric bypass (44.39), or laparoscopic gastric banding (44.99) between January 2006 and December 2017 were identified. Individuals were excluded on the basis of baseline BMI value, diabetes type and date of surgery, such that those with BMI <27.5kg/m^2 (n=228), non-T2DM patients (n=14), with a history of CVD (n=67), history of severe kidney failure defined by estimated glomerular filtration rate (eGFR)<30 ml/min/1.73m^2 (n=20). Index date of patients in bariatric surgery group was defined as the date of first bariatric surgery. A total of 303 patients were observed from the index date until the incidence of event outcome, death from any cause, and censored at the last recorded healthcare utilization date, whichever came first.

Outcome Measures

Our study outcomes were time to the risk of all-cause mortality, composite CVD event (acute myocardial infarction, other ischemic heart disease, congestive heart failure, stroke, and peripheral vascular disease), ESKD, and SH. Dates of death were sourced from The Births and Deaths General Register Office under the Immigration Department of Hong Kong. CVD and SH events were defined based on the diagnosis codes of the ICD-9-CM and the ICPC-2.

All the ICD-9-CM and ICPC-2 diagnosis codes for comorbidities and event outcomes are listed in supplemental table 1.

Other outcomes included the change in eGFR and urine albumin-creatinine ratio (UACR) from baseline to follow-up measurements. The eGFR was estimated by the Modification of Diet in Kidney Disease Study (MDRD) equation based on serum creatinine, race, age and gender [30].

Baseline Covariates

The following baseline covariates were considered: demographic characteristics (age and sex), clinical characteristics, such as BMI, weight, height, waist, HbA1c, systolic and diastolic blood pressure, total cholesterol (TC), high-density lipoprotein (HDL-C), TC/HDL-C ratio, low-density lipoprotein (LDL-C), UACR, serum creatinine, eGFR, duration of T2DM, pre-existing comorbidities (hypertension, mental health problems, hyperlipidaemia, obstructive sleep apnoea, gallbladder disease, musculoskeletal and chronic orthopaedic disorders, prior severe hypoglycaemia), Charlson Comorbidity Index (CCI), and ever dispense of insulin, oral anti-diabetic drugs, anti-hypertensive drugs and lipid lowering agents.

One-to-Five Propensity Score Matching Method

Eligible surgical patients who met the selection criteria were identified and were matched to the control patients according to their propensity scores and cohort entry year (see Supplemental Figure 1). The propensity scores of all enrolled patients were calculated by using multivariable logistic regression adjusting for baseline covariates. These covariates include age, gender, BMI, HbA1c, SBP, DBP, total cholesterol, HDL-C, LDL-C, serum creatinine, UACR, triglyceride, fasting glucose, use of oral anti-diabetic drugs, use of insulin, use of hypertension drugs, use of lipid lowering agents, and history of hypertension, pre-existing comorbidities (mental health problems, hyperlipidaemia, obstructive sleep apnoea, gallbladder disease, musculoskeletal and chronic orthopaedic disorders). The caliper criteria improved the quality of the nearest neighbour matching by specifying a maximum tolerance of the propensity score distance between patients in the surgical group and in the control group. The propensity score matching was performed by 'calipmatch' command on a one-to-five basis without replacement and caliper criteria of 0.05 in STATA.

Statistical Analysis

Descriptive statistics of baseline characteristics were displayed in overall and by bariatric surgery and matched control groups. Comparisons of baseline covariates between the groups were made using independent t-test for continuous variables and Chi-squared test for categorical variables. The balance of baseline covariates between the groups were further assessed with the absolute standardized mean difference (SMD), before and after the propensity score matching. All SMDs were less than 0.2 implying an optimal balance between the groups [31].

To address the missingness of baseline data, multiple imputation by chained equations (MICE) [32] was used for both surgical and control patients. HbA1c, SBP, DBP and LDL-C were imputed by other clinical parameters such as BMI, gender, age, total cholesterol, HDL-C, serum creatinine, UACR, triglyceride fasting glucose, CCI, use of oral anti-diabetic drugs, use of insulin, use of anti-hypertensive drugs, use of lipid lowering agents, and history of mental health problems, hyperlipidaemia, obstructive sleep apnoea, gallbladder disease, musculoskeletal and chronic orthopaedic disorders, and hypertension. Model parameters were estimated from multiply imputed data and then used to obtain multiple-imputation linear predictions by applying Rubin's combination rules observation wise to the completed-data predictions [33]. Propensity Score Matching was performed using the predictions obtained after MICE.

For both groups, mean values of eGFR and UACR at baseline and follow-ups at month 6, 12, 24, 36, 48, 60 were displayed with 95% confidence interval (CI). For each measurement point, relevant clinical parameters recorded between 6 months prior to the measurement point and 6 months post the measurement point were all retrieved. During each time window, readings on the closest date to the measurement point were used for analyses. Changes in values from baseline to follow-ups were assessed by multilevel mixed-effects regression and differences between the two groups were provided.

IRs of each outcome event for each group were estimated using the total number of patients with event occurrence during the follow-up period divided by person-years at risk. To examine the association between the bariatric surgery and incidence of event, Cox proportional hazards regression model was used for multivariable analyses. Hazard ratios (HR) and its 95% CI were reported for each variable in the regression model. Log-rank test

was used to compare the equality of the survival curves between the groups. Predictive accuracy of Cox models was assessed and compared using Harrell's discrimination C-index, ranging from zero to one. A value of 0.5 indicates no predictive discrimination, and values of 0 or 1.0 indicate perfect separation of patients. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. Goodness-of-fit of Cox regression model were assessed using Akaike information criterion and Bayesian information criterion. We further assessed the risk of CVD by subgroups by using cox regression models and examined the effects of interaction between bariatric surgery and baseline characteristics.

All statistical analyses were performed using STATA version 13.0 (StataCorp LP, College Station, Texas), were conducted by two co-authors (CKHW and TTW), and cross-checked for quality assurance. All significance tests were two-tailed and P values <.05 were taken to indicate statistical significance.

Results

The selection process of the cohort group is outlined in the flowchart in Supplemental Figure 1. A total of 303 eligible surgical patients were identified from the database and were matched with 1,399 control patients by using one-to-five propensity score matching method. A majority of surgical patients (80.5%) underwent laparoscopic SG operation followed by laparoscopic RYGB (16.2%) and Laparoscopic GB (3.0%) with a minority of patients (3.6%) receiving a re-operation of laparoscopic RYGB and GB.

Patient characteristics

Table 1 illustrates the baseline socio-demographic and clinical characteristics of diabetes patients who are obese. There were no statistically significant differences in age, gender distribution, history of hypertension, mental health problems, hyperlipidaemia, obstructive sleep apnoea, gallbladder disease, musculoskeletal and chronic orthopaedic disorders, proportion in different CCI categories, and usage of medications. However, patients in bariatric surgery group were found to have significantly greater baseline BMI, weight and height values, as well as CCI scores, than patients in the matched control group. Also, more percentage of patients in the bariatric surgery group had history prior SH than that of patients in the control cohort.

Incidence rates

Table 2 illustrates the number and IRs of all-cause mortality, severe hypoglycaemia, CVD, stage 4/5 chronic kidney disease and ESKD events of obese T2DM patients. Over a mean follow-up period of 32 months with 5725 person-years, 0, 15 and 5 incidence of all-cause mortality, stage 4/5 chronic kidney disease and ESKD occurred respectively, 6 patients had an episode of SH and 11 patients were diagnosed with CVD. Higher cumulative incidences of CVD, all-cause mortality and SH were reported in matched control group. The IRs of CVD, mortality and SH (2.814, 1.954, 1.485/100 person-years) in control group were found to be higher than that in surgical group (1.321, 0, 0.706/100 person-years). A total of 95 cases in the matched control group died during the post-surgery period, while there were no death records in the bariatric surgery group. A total of 18 out of 95 (18.95%) deaths in the matched control group had no records of causes of death. Apart from these 18 cases, 29 (37.66%), 20 (25.97%), 11 (14.29%), 7 (9.09%), 5 (6.49%) and 2 (2.60%) patients died from cancer, heart diseases, respiratory diseases (mainly Pneumonia), infectious diseases, kidney diseases and digestive diseases, respectively.

Hazard ratios

Figure 1 presents Kaplan Meier survival curves for all-cause mortality, SH, CVD events, stage 4/5 chronic kidney disease and ESKD for patients in both groups. Table 4 reports the HR of all-cause mortality, SH, CVD, stage 4/5 chronic kidney disease and ESKD events for bariatric surgery versus matched control.

Significant differences between two groups were present for the risk of CVD events (HR=0.464, CI=0.251-0.860, p=0.015). Risk of SH (HR=0.469, CI=0.204-1.81, p=0.076), stage 4/5 chronic kidney disease (HR=0.896, CI=0.519-1.545, p=0.692) and ESKD (HR=0.666, CI=0.264-1.683, p=0.390) was not significantly lowered after surgery. There was no occurrence of all-cause mortality after surgery.

A subgroup analysis of cox regression was performed on CVD for bariatric surgery versus matched control with the results shown in Table 4. Interaction effects between bariatric surgery and two baseline characteristics were examined. History of hypertension (P-interaction=0.019) and eGFR categories at baseline (P-interaction=0.050) significantly modified the effects of bariatric surgery on CVD events. Indeed, compared with matched

control patients, surgical patients with history of hypertension, or CCI >3 had significantly reduced the risk of CVD (HR=0.301, CI=0.132-0.688, p=0.004; HR=0.389, CI=0.156-0.972, p=0.043). Although the p-interaction was not significant for patients in different BMI categories, the benefit of surgery was the most prominent in patients with BMI ≥40 kg/m^2 as demonstrated by a profound reduction in the risk of CVD events (HR=0.118, CI=0.016-0.868, p=0.036). None of the subgroups were associated with significant reduction in kidney outcomes, SH and all-mortality risks after bariatric surgery (not shown).

Changes in kidney outcomes

Figure 2 depicts the changes of eGFR and UACR over 5-year follow-up period.

The mean eGFR of patients in matched control group showed a decreasing trend across 60 months. For surgical patients, their eGFR increased slightly from 99.37 ml/min/1.73m^2 at baseline to 100.37 ml/min/1.73m^2 at month 12, and then went down to 91.30 ml/min/1.73m^2 at the end of follow-up. Overall, the mean eGFR level of surgical patients were higher than that of non-surgical peers after baseline, and the differences were significant at 6 and 12 months.

The changes of UACR for both groups fluctuated between 6.03 ug/mg and 29.83ug/mg over time. The UACR level of surgical patients were significantly lower than that of control patients at 6, 12, 24 and 48 months.

Discussion

This study is the population-based cohort study in assessing risks of post-bariatric surgery hypoglycemia, CVD, ESKD, and all-cause mortality. Findings of this study addressed the research gap in enhancing our knowledge in understanding the benefits of surgery, as providing an effective mean of disease management and addressing the increasing disease burden of patients with co-existence of obesity and T2DM.

Based on this population-based cohort with a maximum follow-up period of 10 years, laparoscopic SG was the most performed surgery followed by laparoscopic RYGB and laparoscopic GB. A considerable number of operations was performed on patients who were severely obese and morbidly obese with a BMI 35-40kg/m^2 (Class II) and >40kg/m^2 (Class

III). A possible explanation for this might be that surgical operation is likely to be more clinically indicated for these patients considering the financial cost. Attaining euglycemia and sustained weight loss are known to be frequently challenging [34]. Our results showed a significant reduction of CVD and a possible benefit in all-cause mortality and SH for those received bariatric surgery. These results were consistent with the reduced hazard risks obtained, whereby surgery was effective in lowering the risks of all-cause mortality and cardiovascular events. In other words, the study data suggested a possible cardio-protective effect of bariatric surgery and were in line with prospectively conducted SOS study [16, 17, 35]. The evidence corroborates the guidelines from the ACC [7], ADA and the IDF [8]. Likewise, the findings match to those observed in an earlier retrospective study which examined the cardiovascular benefits of RYGB specifically [6]. When the risk of CVD was further assessed in subgroup analysis, the most striking result to emerge from the data is that there was more than 90% risk reduction in CVD for patients who are morbidly obese compared to those with conventional treatment. This finding is in line with that of another retrospective cohort study, specifically focused on patients who are moderate and severely obese in the US. In this study, a 60-70% reduction in the HR of cardiovascular events was observed in patients across a median follow up time of less than 2 years [36].

Our study was further examined by considering the effects of interaction. Among all groups of patients, those who are morbidly obese had most significantly greater reduction in CVD risk compared with other patients who have a lower BMI in the control group. These results further support the idea that bariatric surgery is most effective targeting towards the morbidly diabetes patients who are obese. Besides, the fact that surgery exerted a positive influence in risk reduction of patients with hypertension history in this study, reinforced its cardio-protective effect of surgery since hypertension is known as a risk factor for CVD. The results are in agreement with that Douglas' [37] and Rubio-Almanza's [38] findings which showed a positive association between two and that surgery was beneficial with a sustained risk reduction over 5 years. Apart from Wei's study [19], few have examined the associated cardiovascular effects among Chinese patients through a prospective study with 1-year follow up period. The 10-year disease risk was calculated using the UKPDS risk engine [39]. Though findings were significant, it is important to be aware that this risk engine has been used as a CHD risk assessment tool in diabetes patients based on data from patients in the UK. Thus, it is likely that the system may not be applicable to that of Chinese population.

Our study also supported that bariatric surgery has protective kidney effect in obese patients. Although the results were not significantly different, risks of stage 4/5 chronic kidney diseases and ESKD of surgical patients tended to be lower than those of non-surgical peers, consistent with previous large longitudinal cohort studies that concluded that the use of bariatric surgery prevented and reduced the progression of chronic kidney diseases and ESKD [20, 22, 40]. Bariatric surgery resulted in significant improvements in eGFR up to 36 months, echoing the main finding from a retrospective propensity score matched cohort study [41].

Our study showed that risk of SH in bariatric surgery group was not significantly different from that in matched control group, although surgical patients tended to have lower IR of SH. However, a previous population-based cohort study demonstrated a higher risk of SH in bariatric surgery [25]. Despite the conflicting evidence for the SH risks, both studies showed that there was no significant difference between surgery and control patients in risks of SH. Therefore, bariatric surgery overall is safe in the aspect that it did not increase the incidence of SH.

Although the study strengthened our understanding of the effects of bariatric surgery on risk reduction of all-cause mortality and CVD events, limitations existed. The effects of lifestyle risk factors towards the outcomes were not taken into account in analysis since these factors were not routinely captured by clinical management system database for propensity score matching. In addition, time-varying factors, such as changes in HbA1c, blood pressure, lipid profile and use of medications (e.g. glucose lowering medications, anti-hypertensive agents, renin–angiotensin–aldosterone system blockers), were also not considered in the propensity score matching and subsequent multivariable analyses. These could potentially exert an influence on the risks of CVD adverse effects and affecting the validity of results. Besides, since fewer data were available in year 4 onwards, the power to detect significant difference of eGFR and UACR between surgery and control group was limited. Moreover, IR of all-cause mortality for surgical patients were found to be zero in this study. It is possible this was due to quality of surgical techniques or post-operative care in Hong Kong, so that this study did not detect any surgical patient turning to deaths. In a previous cohort study in Hong Kong, no deaths were reported as well [42]. However, the propensity score methodology was applied to isolate any residual confounders and balance the baseline characteristics between the groups. Nevertheless, we cannot exclude the underlying bias that patients in the surgery

group were inherently different from non-surgical peers, since they were initially approved for bariatric surgery by surgeons while controls were not. In addition, risks of post-bariatric SH vary by types of bariatric surgery [25, 26]. However, we did not differentiate the type of bariatric surgery. Finally, as our data were extracted from HA, which manages public healthcare services in Hong Kong, we were unable to analyse patients who turned to private sectors or left Hong Kong.

In conclusion, this propensity-score matched population-based cohort study determined benefits of bariatric surgery towards lowering the risks of CVD and all-cause mortality events for Chinese patients who are obese with diabetes. While risk of stage 4/5 chronic renal diseases and ESKD were not significantly different between surgery and non-surgery groups, our findings on long-term changes in eGFR suggest benefit of bariatric surgery on kidney outcomes.

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Conflict of Interest Statement

Authors declare that they have no relevant financial interests.

Authors' Contributions

C.W. constructed the study design. C.W. and TTW conducted the data analysis. C.W. and TTW was responsible for the paper draft and data interpretation. S.W., B.L., E.G., E.N., O.W., and C.L were responsible for expertise advice and final approval. All authors read and approved the final manuscript.

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Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval of this study was granted by Institutional Review Board of the University of Hong Kong /Hospital Authority Hong Kong West Cluster (Ref No. UW 16-1018).

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Table 1. Baseline socio-demographic and Clinical Characteristics of obese type 2 diabetes mellitus patients with and without bariatric surgery

Baseline Characteristics	Before matching	1-to-5 propensity score matching			
	Bariatric Surgery Participants	Bariatric Surgery Participants	Control Participants		
	Total (N=335) %	Total (N=303) %	Total (N=1399) %	P-value	SMD†
Socio-demographic					
Sex				0.924	0.006
Female	53.1	54.1	53.8		
Male	46.9	45.9	46.2		
Age (mean±SD), year	51.21 ± 12.45	51.35 ± 12.26	50.98 ± 13.44	0.653	0.029
Clinical (mean±SD) ¶					
BMI, kg/m^2	37.75 ± 5.26	37.44 ± 5.04	36.55 ± 6.49	0.024*	0.154
Weight, kg	102.38 ± 18.71	101.39 ± 17.91	95.13 ± 20.33	<0.001*	0.327*
Height, m	1.64 ± 0.09	1.64 ± 0.09	1.61 ± 0.11	<0.001*	0.314*
HbA1c, %	7.67 ± 1.56	7.67 ± 1.53	7.68 ± 1.85	0.929	0.006
Systolic blood pressure, mmHg	134.14 ± 16.50	134.19 ± 16.61	134.50 ± 15.93	0.793	0.018
Diastolic blood pressure, mmHg	77.95 ± 9.89	77.98 ± 9.92	78.16 ± 10.29	0.805	0.018
Total cholesterol, mmol/L	4.38 ± 0.90	4.37 ± 0.86	4.39 ± 0.89	0.636	0.031
HDL-C, mmol/L	1.10 ± 0.28	1.11 ± 0.28	1.11 ± 0.28	0.902	0.008
TC/HDL-C ratio	4.24 ± 1.56	4.15 ± 1.23	4.16 ± 1.23	0.896	0.008
LDL-C, mmol/L	2.45 ± 0.79	2.44 ± 0.75	2.45 ± 0.75	0.861	0.011
Urine ACR	17.85 ± 45.32	18.92 ± 47.07	13.21 ± 40.44	0.061	0.130
Creatinine (Serum), umol/L	72.32 ± 21.74	73.03 ± 22.28	71.91 ± 20.20	0.391	0.053
eGFR, ml/min/1.73m^2	98.79 ± 27.92	97.39 ± 27.14	99.07 ± 34.47	0.424	0.054
Duration of DM, year (mean±SD)	3.85 ± 3.11	3.97 ± 3.17	4.08 ± 2.81	0.554	0.036
Duration of DM, year				0.051	0.139
≤5 years	65.4	64.4	66.8		
5-<10 years	29.3	29.7	30.2		

>10 years	5.4	5.9	3.1		
History of Hypertension	79.1	78.5	78.3	0.915	0.007
History of Mental health problems	5.1	4.6	5.7	0.448	0.050
History of Hyperlipidaemia	50.2	47.5	49.0	0.650	0.029
History of Obstructive sleep apnoea	57.9	55.8	55.5	0.922	0.006
History of Gall bladder disease	9.0	8.9	7.9	0.572	0.035

Table 1. Baseline socio-demographic and Clinical Characteristics of obese patients with type 2 diabetes mellitus (Cont.)

History of Musculoskeletal and chronic orthopaedic disorders	23.6	24.8	23.4	0.608	0.032
History of Prior severe hypoglycaemia	13.1	13.2	9.0	0.026*	0.134
Charlson Comorbidity Index (mean±SD)	3.21 ± 1.51	3.22 ± 1.50	2.95 ± 1.43	0.004*	0.179
Charlson Comorbidity Index				0.153	0.090
≤3	65.4	64.7	68.9		
>3	34.6	35.3	31.1		
Insulin ever used	19.1	18.8	18.9	0.958	0.003
Oral anti-diabetic drugs ever used	55.2	59.1	62.0	0.348	0.059
Anti-hypertensive drugs ever used	75.8	77.6	77.1	0.850	0.012
Lipid lowering agents ever used	50.2	49.8	52.8	0.357	0.058
Cohort entry year				0.948	0.038
2006-2010	13.1	11.6	10.5		
2011-2013	20.9	20.8	21.7		
2014-2015	23.3	24.1	23.9		
2016-2017	42.7	43.6	43.8		

Note:
Abbreviations: SMD = standardized mean difference; SD = Standard deviation; BMI = Body mass index; HbA1c = Haemoglobin A1c; HDL-C = High-Density Lipoprotein Cholesterol; TC = Total cholesterol; LDL-C = Low-Density Lipoprotein Cholesterol; eGFR = estimated Glomerular Filtration Rate; DM = Diabetes Mellitus

¶ Laboratory results at baseline is defined as laboratory results collected on the closest date before the surgery date

* Significant differences (P < 0.05) by independent t-test or by chi-square test, as appropriate

† Imbalance covariate if the ASMD >= 0.2

Table 2. Number and incidence rate of all-cause mortality, cardiovascular diseases, severe hypoglycaemia disease, stage 4 or 5 chronic kidney disease and end-stage kidney disease events

	Cumulative incidence		Incidence rate (Cases/ 100 person-years)			Median follow-up	Mean follow-up
Event	Cases with event	Rate	Estimate	95% CI*	Person-years	periods (Months)	periods (Months)
Total (N= 1702)							
All-cause mortality	95	0.056	1.660	(1.343, 2.029)	5724.58	32	40
Severe hypoglycaemia	75	0.044	1.365	(1.073, 1.711)	5496.17	26	39
Cardiovascular diseases	139	0.082	2.583	(2.171, 3.050)	5381.83	25	38
Acute myocardial infarction	23	0.014	0.405	(0.257, 0.607)	5684.17	31	40
Other ischemic heart disease	46	0.027	0.820	(0.600, 1.094)	5608.58	31	40
Congestive heart failure	41	0.024	0.727	(0.522, 0.986)	5639.33	31	40
Stroke	55	0.032	0.983	(0.740, 1.279)	5596.00	29	39
Peripheral vascular disease	17	0.010	0.299	(0.174, 0.479)	5676.83	31	40
Stage 4 or 5 chronic kidney disease	111	0.065	1.991	(1.638, 2.398)	5574.08	28	39
End-stage kidney disease	49	0.029	0.865	(0.640, 1.144)	5664.92	31	40
Bariatric surgery (N=303)							
All-cause mortality	0	0.000	0.000	NA	862.83	24	34
Severe hypoglycaemia	6	0.020	0.706	(0.259, 1.537)	849.42	23	34
Cardiovascular diseases	11	0.036	1.321	(0.659, 2.363)	832.83	23	33
Acute myocardial infarction	2	0.007	0.232	(0.028, 0.839)	861.25	24	34
Other ischemic heart disease	3	0.010	0.350	(0.072, 1.022)	857.67	23	34

Congestive heart failure	2	0.007	0.233	(0.028, 0.842)	858.00	23	34
Stroke	7	0.023	0.828	(0.333, 1.705)	845.67	24	33
Peripheral vascular disease	1	0.003	0.116	(0.003, 0.648)	859.92	23	34
Stage 4 or 5 chronic kidney disease	15	0.050	1.784	(0.998, 2.942)	841.00	23	33
End-stage kidney disease	5	0.017	0.587	(0.190, 1.369)	852.42	23	34
Matched control (N= 1399)							
All-cause mortality	95	0.068	1.954	(1.581, 2.389)	4861.75	34	42
Severe hypoglycaemia	69	0.049	1.485	(1.155, 1.879)	4646.75	30	40
Cardiovascular diseases	128	0.091	2.814	(2.347, 3.346)	4549.00	28	39
Acute myocardial infarction	21	0.015	0.435	(0.270, 0.666)	4822.92	34	41
Other ischemic heart disease	43	0.031	0.905	(0.655, 1.219)	4750.92	34	41
Congestive heart failure	39	0.028	0.816	(0.580, 1.115)	4781.33	34	41
Stroke	48	0.034	1.010	(0.745, 1.340)	4750.33	33	41
Peripheral vascular disease	16	0.011	0.332	(0.190, 0.539)	4816.92	34	41
Stage 4 or 5 chronic kidney disease	96	0.069	2.028	(1.643, 2.477)	4733.08	33	41
End-stage kidney disease	44	0.031	0.914	(0.664, 1.227)	4812.50	34	41

Note: Abbreviation: CI = Confidence interval

Table 3. Hazard ratio of all-cause mortality, cardiovascular diseases, severe hypoglycaemia, stage 4 or 5 chronic kidney disease and end-stage kidney disease for bariatric surgery versus matched control

Event	Bariatric surgery vs matched control		
	Hazard ratio	95% CI	P-value
All-cause mortality	NA	NA	NA
Severe hypoglycaemia	0.469	(0.204, 1.081)	0.076
Cardiovascular diseases	0.464	(0.251, 0.860)	0.015*
Acute myocardial infarction	0.534	(0.125, 2.278)	0.397
Other ischemic heart disease	0.386	(0.120, 1.246)	0.111
Congestive heart failure	0.811	(0.367, 1.793)	0.605
Stroke	0.283	(0.068, 1.173)	0.082
Peripheral vascular disease	0.382	(0.050, 2.899)	0.352
Stage 4 or 5 chronic kidney disease	0.896	(0.519, 1.545)	0.692
End-stage kidney disease	0.666	(0.264, 1.683)	0.390

Note: Abbreviation: CI = Confidence interval

* Significant difference with P-value < 0.05

Table 4. Sub-group analysis of hazard ratio of cardiovascular diseases for bariatric surgery versus matched control

Event	Bariatric surgery vs matched control			
	HR	95% CI	P-value	Interaction P-value
Overall	0.464	(0.251, 0.860)	0.015*	
Gender				0.620
Female	0.477	(0.206, 1.104)	0.084	
Male	0.435	(0.174, 1.084)	0.074	
Age category				0.195
<60	0.457	(0.220, 0.949)	0.036*	
≥60	0.830	(0.258, 2.672)	0.754	
BMI category				0.059
30-<40 kg/m^2	0.631	(0.328, 1.212)	0.166	
≥40 kg/m^2	0.118	(0.016, 0.868)	0.036*	
Duration of DM				0.147
≤5 years	0.519	(0.261, 1.032)	0.061	
>5 years	0.306	(0.073, 1.276)	0.104	
Glycaemic control				0.277
HbA1c≤7	0.323	(0.101, 1.037)	0.058	
HbA1c>7	0.529	(0.255, 1.098)	0.087	
History of hypertension				0.019*
Yes	0.301	(0.132, 0.688)	0.004*	
No	1.143	(0.434, 3.013)	0.787	
Charlson comorbidity index				0.189
≤3	0.511	(0.221, 1.183)	0.117	
>3	0.389	(0.156, 0.972)	0.043*	
Oral anti-diabetic drugs ever used				0.680
Yes	0.666	(0.319, 1.391)	0.279	
No	0.237	(0.074, 0.756)	0.015*	
Metformin ever used				0.815
Yes	0.751	(0.340, 1.660)	0.480	
No	0.259	(0.094, 0.709)	0.009*	
Anti-hypertensive drugs ever used				0.541
Yes	0.490	(0.237, 1.014)	0.055	
No	0.371	(0.114, 1.204)	0.099	
Lipid lowering agents ever used				0.317
Yes	0.482	(0.209, 1.115)	0.088	
No	0.426	(0.170, 1.065)	0.068	
eGFR categories				0.050*
eGFR ≥ 90 mL/min/1.73m^2 †	0.240	(0.075, 0.767)	0.016*	0.055
eGFR = 60-<90 mL/min/1.73m^2 ‡	0.693	(0.274, 1.751)	0.438	0.875
eGFR = 30-<60 mL/min/1.73m^2	0.549	(0.160, 1.886)	0.341	

Note: Abbreviations: HR = Hazard ratio; CI = Confidence interval; BMI = Body mass index; DM = Diabetes Mellitus; CKD = Chronic Kidney Disease; eGFR = estimated Glomerular Filtration Rate

†: The interaction P-value of eGFR≥ 90 mL/min/1.73m^2 versus eGFR of 30-<60 mL/min/1.73m^2

‡: The interaction P-value of eGFR = 60-<90 mL/min/1.73m^2 versus eGFR of 30-<60 mL/min/1.73m^2

*: Significant difference with P-value < 0.05

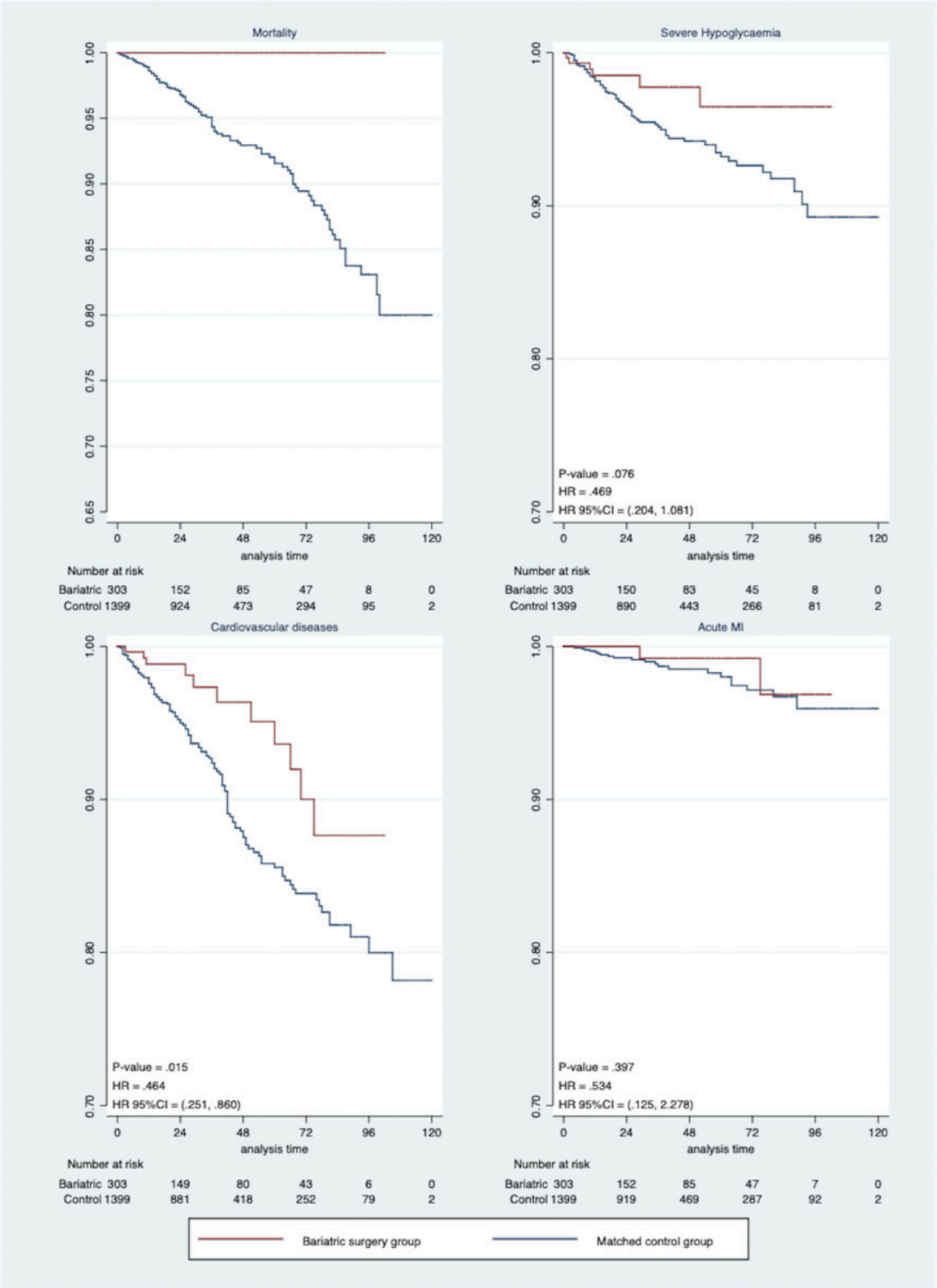
#: Not applicable due to no observations

Figure legends:

Figure 1 Kaplan Meier survival curves for all-cause mortality, severe hypoglycemia, cardiovascular diseases, acute myocardial infarction, other ischemic heart disease, congestive heart failure, stroke, peripheral vascular disease, severe chronic kidney disease and end-stage kidney disease for type 2 diabetes mellitus patients in bariatric surgery group or matched control group after propensity score matching

Figure 2 Changes in estimated Glomerular Filtration Rate and urine Albumi/Creatinine Ratio over time

FIGURE 1: Kaplan–Meier survival curves for all-cause mortality, SH, CVDs, acute MI, other ischaemic heart disease, congestive heart failure, stroke, peripheral vascular disease, severe CKD and ESKD for T2DM patients in the bariatric surgery group or the matched control group after propensity score matching.



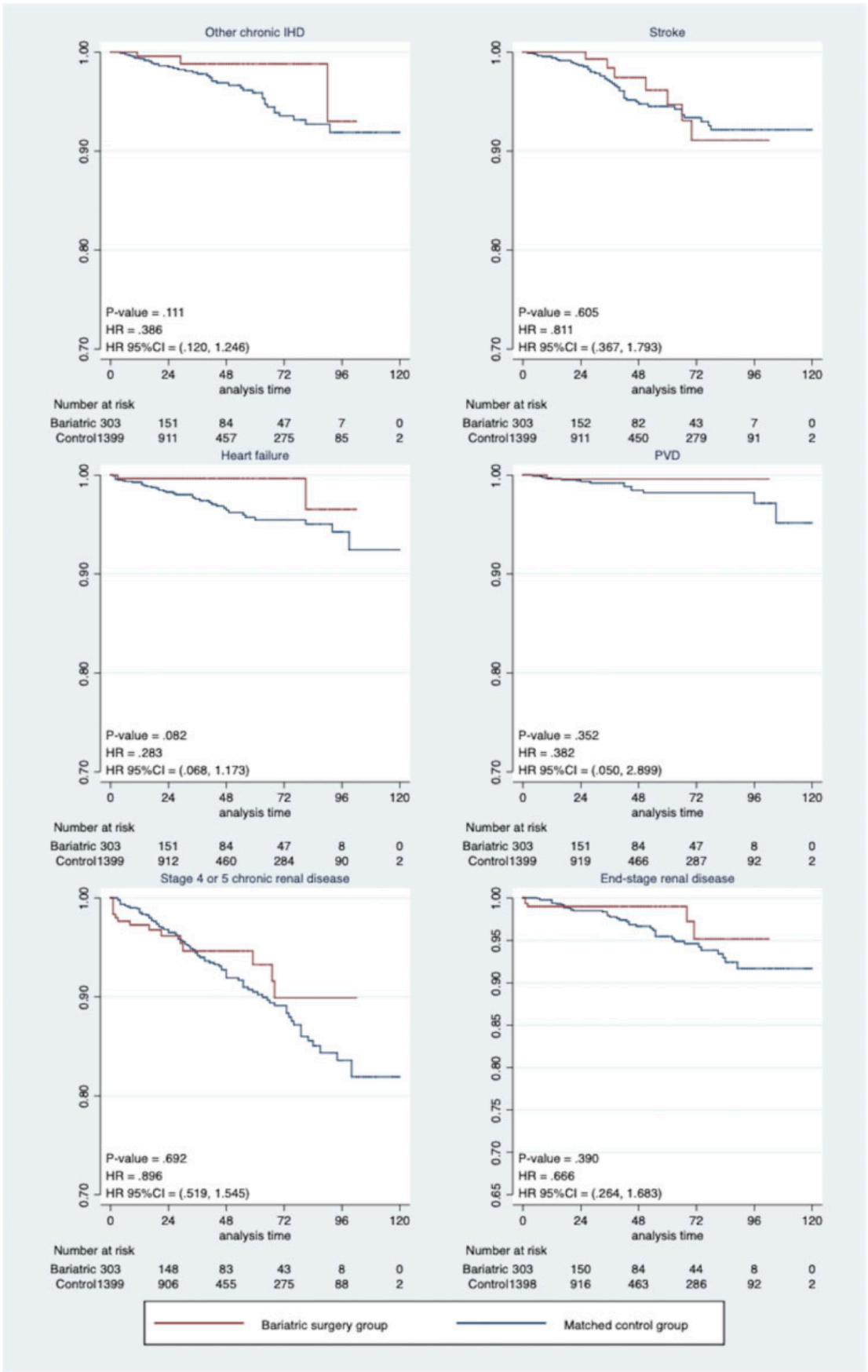

Other chronic IHD
1.00
0.90
0.80
0.70
P-value = .111
HR = .386
HR 95%CI = (.120, 1.246)
0 24 48 72 96 120
analysis time
Number at risk
Bariatric 303 151 84 47 7 0
Control 1399 911 457 275 85 2
Stroke
1.00
0.90
0.80
0.70
P-value = .605
HR = .811
HR 95%CI = (.367, 1.793)
0 24 48 72 96 120
analysis time
Number at risk
Bariatric 303 152 82 43 7 0
Control 1399 911 450 279 91 2
Heart failure
1.00
0.90
0.80
0.70
P-value = .082
HR = .283
HR 95%CI = (.068, 1.173)
0 24 48 72 96 120
analysis time
Number at risk
Bariatric 303 151 84 47 8 0
Control 1399 912 460 284 90 2
PVD
1.00
0.90
0.80
0.70
P-value = .352
HR = .382
HR 95%CI = (.050, 2.899)
0 24 48 72 96 120
analysis time
Number at risk
Bariatric 303 151 84 47 8 0
Control 1399 919 466 287 92 2
Stage 4 or 5 chronic renal disease
1.00
0.90
0.80
0.70
P-value = .692
HR = .896
HR 95%CI = (.519, 1.545)
0 24 48 72 96 120
analysis time
Number at risk
Bariatric 303 148 83 43 8 0
Control 1399 906 455 275 88 2
End-stage renal disease
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
P-value = .390
HR = .666
HR 95%CI = (.264, 1.683)
0 24 48 72 96 120
analysis time
Number at risk
Bariatric 303 150 84 44 8 0
Control 1398 916 463 286 92 2
Bariatric surgery group
Matched control group

FIGURE 2: Changes in eGFR and UACR over time.