Renal and Cardiovascular Outcomes After Weight Loss From Gastric Bypass Surgery in Type 2 Diabetes: Cardiorenal Risk Reductions Exceed Atherosclerotic Benefits

Vasileios Liakopoulos,[1,2] Stefan Franzén,[3,4] Ann-Marie Svensson,[1,3] Naveed Sattar,[5] Mervete Miftaraj,[3] Staffan Björck,[3] Johan Ottosson,[6] Ingmar Näslund,[6] Soffia Gudbjörnsdottir,[1,3] and Björn Eliasson[1,2]

Diabetes Care 2020;43:1276–1284 | https://doi.org/10.2337/dc19-1703

OBJECTIVE

We examined detailed renal and cardiovascular (CV) outcomes after gastric bypass (GBP) surgery in people with obesity and type 2 diabetes mellitus (T2DM), across several renal function categories, in a nationwide cohort study.

RESEARCH DESIGN AND METHODS

We linked data from the National Diabetes Register and the Scandinavian Obesity Surgery Register with four national databases holding information on socioeconomic variables, medications, hospitalizations, and causes of death and matched 5,321 individuals with T2DM who had undergone GBP with 5,321 who had not (age 18–65 years, mean BMI >40 kg/m^2, mean follow-up >4.5 years). The risks of postoperative outcomes were assessed with Cox regression models.

RESULTS

During the first years postsurgery, there were small reductions in creatinine and albuminuria and stable estimated glomerular filtration rate (eGFR) in the GBP group. The incidence rates of most outcomes relating to renal function, CV disease, and mortality were lower after GBP, being particularly marked for heart failure (hazard ratio [HR] 0.33 [95% CI 0.24, 0.46]) and CV mortality (HR 0.36 [(95% CI 0.22, 0.58]). The risk of a composite of severe renal disease or halved eGFR was 0.56 (95% CI 0.44, 0.71), whereas nonfatal CV risk was lowered less (HR 0.82 [95% CI 0.70, 0.97]) after GBP. Risks for key outcomes were generally lower after GBP in all eGFR strata, including in individuals with eGFR <30 mL/min/1.73 m^2.

CONCLUSIONS

Our data suggest robust benefits for renal outcomes, heart failure, and CV mortality after GBP in individuals with obesity and T2DM. These results suggest that marked weight loss yields important benefits, particularly on the cardiorenal axis (including slowing progression to end-stage renal disease), whatever the baseline renal function status.

[1]Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden
[2]Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[3]National Diabetes Register, Center of Registers, Gothenburg, Sweden
[4]Health Metrics Unit, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[5]The Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.
[6]Department of Surgery, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Corresponding author: Vasileios Liakopoulos, vasileios.liakopoulos@vgregion.se

Received 24 August 2019 and accepted 22 January 2020

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1703/-/DC1.

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetescore-update-podcasts.

© 2020 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/content/license.

See accompanying article, p. 1175.

Obesity and type 2 diabetes mellitus (T2DM) are two of the most serious and accelerating public health scourges worldwide (1,2). Cardiovascular disease (CVD) and renal disease have been strongly linked to both of them (3,4). The risk of end-stage renal disease is significantly elevated in patients who have severe obesity with or without diabetes (5). It is well known that severe obesity, independently of diabetes, is associated with greater incidence of proteinuria, which can progress to chronic kidney disease (CKD) (6). This relationship is complex and not yet fully understood. Mechanisms such as elevated blood pressure or glucose, hyperinsulinemia, inflammation, the effects of glomerular hyperfiltration and focal or segmental glomerulosclerosis have been suggested (7). However, to what extent large weight loss can lessen important renal outcomes is not fully established.

Bariatric surgery, especially Roux-en-Y gastric bypass (GBP), is currently the most efficient method of treating obesity, with beneficial effects long-term (8,9). Except for sustained weight loss, the beneficial effects on HbA_{1c}, triglyceride levels, HDL and LDL cholesterol, and blood pressure have been presented in both observational (10,11) and randomized studies (12,13). The adverse effects of GBP for various follow-up periods of investigation have also been demonstrated (14,15). However, the effects of bariatric surgery, GBP, and weight loss on renal function and its progression, as well as the entity of risk factors/predictors for renal dysfunction, have been poorly investigated, particularly in patients with T2DM and obesity. Also, given evidence that obesity is more strongly linked to risk for fatal CVD events (16) and incident heart failure (17) than to nonfatal myocardial infarction, we were interested in comparing and contrasting the effects of large weight loss after GBP on cardiorenal outcomes versus atherosclerotic ones.

We therefore designed this nationwide, observational cohort study to investigate the potential effects of GBP on renal disease per se and other cardiorenal outcomes versus CVD outcomes at various levels of renal function in patients with obesity and T2DM compared with matched individuals who had not undergone GBP. Our hypothesis was that possible benefits on renal, heart failure, and CVD mortality outcomes would be larger than effects on nonfatal CVD outcomes.

RESEARCH DESIGN AND METHODS

This observational cohort study was based on the merging of two nationwide quality registers in Sweden: the National Diabetes Register (NDR) and the Scandinavian Obesity Surgery Register (SOReg). We also linked the Swedish Inpatient Register, the Cause of Death Register, and the Prescribed Drug Register, which are administered by the Swedish Board of Health and Welfare, as well as Statistics Sweden. These four databases have complete national coverage and are publicly funded (18,19).

The NDR, which was initiated by the Swedish Society for Diabetology in 1996, contains information on ~90–95% of all patients with diabetes. Physicians and diabetes nurses report clinical information, blood tests, and various measurements from outpatient clinics and primary care centers nationwide at least once a year. Since 2007, the SOReg has recorded >98% of all bariatric surgical procedures and follow-ups (up to 10 years) and is operated by the Swedish Association for Upper Abdominal Surgery. The Swedish Inpatient Register, started in 1987, contains information on all hospitalizations (dates and diagnoses); the Cause of Death Register provides information on all death dates and causes of death since 1961; and the Prescribed Drug Register holds information on all filled prescriptions in all pharmacies after 1 July 2005. Statistics Sweden provides socioeconomic data since 1990. Before entry in the register, all patients have given consent to registration and thus approved that their data may be used for research. The Regional Ethical Review Board of Gothenburg, Sweden, approved this study.

Merging data from the SOReg and NDR (1 January 2007–31 December 2015) provided us with the study population, which consisted of adults (age 18–75 years) with T2DM and obesity who had been treated with GBP. The definition of T2DM was based on epidemiological criteria: treatment with diet, with or without oral antihyperglycemic agents, insulin, or various combinations, as well as patients >40 years of age at the time of diagnosis.

The patients were matched with an equal proportion of patients from the NDR who had not received surgery. Control patients met the criteria of the treated group and were assigned the same index date. We used propensity score matching that was based on sex, age, BMI, and calendar time. A secondary analysis also compared our groups through stratified estimated glomerular filtration rate (eGFR) levels.

To assess renal function, we used eGFR according to both the MDRD and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (20). Microalbuminuria was defined as a urine albumin/creatinine ratio (ACR) of 3–30 mg/mmol and macroalbuminuria as an ACR >30 mg/mmol. We also used the serum creatinine values in millimoles per liter. All laboratory data and measurements were derived from NDR and SOReg. The proportions of missing data were 43% for microalbuminuria, 39% for macroalbuminuria, 37% for physical activity, 31% for LDL cholesterol, 23% for eGFR, 21% for smoking, 20% for systolic blood pressure levels, and 16% for HbA_{1c}.

We assessed the time to renal dysfunction in terms of development of macroalbuminuria, halved eGFR compared with baseline, or renal disease diagnoses as provided from ICD-10 and the Swedish Inpatient Register (Supplementary Table 1). We studied renal disease diagnoses (acute and chronic kidney failure, hemodialysis and peritoneal dialysis, kidney transplant, diabetic nephropathy) that patients received after discharge from the hospital or until the end of the study in December 2015. We were secondarily interested in CV diagnoses, heart failure, and mortality as well as in factors that predict those outcomes.

Statistical Analysis

The baseline characteristics were described by absolute frequencies or mean values with percentages or SDs, respectively. The observed distributions of baseline variables were compared between the groups using standardized mean differences, where we regarded differences of <0.1 as acceptable.

Control patients were matched 1:1 to GBP patients on the basis of the estimated propensity score (21) from a Cox regression model with time-updated data, where exposure for GBP was the end point. The model included sex, age, BMI, and time as a chronological selection of control patients.

End points were evaluated using the number of events and incidence rates per 10,000 person-years together with exact 95% Poisson CIs. Comparisons between GBP and control patients were expressed as hazard ratios (HRs) and conducted

Table 1—Baseline clinical characteristics, including medical history, medications, and socioeconomic variables

	Group, *n* (%) or mean (SD)		
Characteristic	GBP (n = 5,321)	Control (n = 5,321)	Standardized difference
Male sex	2,098 (39.43)	1,926 (36.20)	0.0472
Age (years)	49.0 (9.5)	47.1 (11.5)	0.1220
BMI (kg/m^2)	42.0 (5.7)	40.9 (7.3)	0.1167
HbA_{1c} (mmol/mol)	59.9 (16.9)	58.5 (16.9)	0.0589
Creatinine (mmol/L)	68.1 (27.6)	68.0 (25.4)	0.0026
eGFR (MDRD) (mL/min/1.73 m^2)	97.2 (25.0)	98.3 (27.5)	0.0282
eGFR (CKD-EPI) (mL/min/1.73 m^2)	99.4 (17.6)	100.1 (20.1)	0.0250
LDL (mmol/L)	2.8 (0.9)	2.8 (0.9)	0.0463
HDL (mmol/L)	1.1 (0.3)	1.1 (0.3)	0.0629
Triglycerides (mmol/L)	2.3 (1.5)	2.2 (1.5)	0.0347
Total cholesterol (mmol/L)	4.9 (1.1)	4.9 (1.1)	0.0297
Systolic blood pressure (mmHg)	132.8 (14.5)	132.5 (15.6)	0.0135
Diastolic blood pressure (mmHg)	80.3 (9.6)	80.0 (9.8)	0.0209
Coronary heart disease	395 (7.42)	313 (5.88)	0.0437
CVD	475 (8.93)	408 (7.67)	0.0323
Stroke	109 (2.05)	103 (1.94)	0.0057
Congestive heart failure	142 (2.67)	166 (3.12)	0.0190
Microalbuminuria	481 (19.30)	697 (19.50)	0.0035
Macroalbuminuria	199 (7.50)	298 (7.89)	0.0103
Acute kidney failure	31 (0.58)	50 (0.94)	0.0291
CKD	21 (0.39)	37 (0.70)	0.0289
Diabetic nephropathy	37 (0.70)	43 (0.81)	0.0092
Severe renal disease	56 (1.05)	83 (1.56)	0.0316
Liver disease	16 (0.30)	26 (0.49)	0.0212
Cancer	111 (2.09)	158 (2.97)	0.0398
Psychiatric disorders	520 (9.77)	529 (9.94)	0.0040
Alcohol abuse	94 (1.77)	122 (2.29)	0.0264
Medication			
Blood pressure medication	2,504 (66.23)	3,034 (60.41)	0.0854
Lipid-lowering drugs	2,688 (50.52)	2,414 (45.37)	0.0730
Insulin	1,967 (36.97)	1,886 (35.44)	0.0224
Metformin	3,947 (74.18)	3,769 (70.83)	0.0530
Sulfonylureas	627 (11.78)	541 (10.17)	0.0366
α-Glucosidase inhibitors	41 (0.77)	38 (0.71)	0.0046
Meglitinides	138 (2.59)	132 (2.48)	0.0051
Glitazones	190 (3.57)	150 (2.82)	0.0302
DPP-4 inhibitors	257 (4.83)	239 (4.49)	0.0113
GLP-1 analogs	310 (5.83)	245 (4.60)	0.0389
SGLT2 inhibitors	1 (0.02)	1 (0.02)	0.0000
NSAIDs	1,852 (34.81)	1,476 (27.74)	0.1081
Opiates	1,658 (31.16)	1,026 (19.28)	0.1952
Physical activity			
Never	551 (20.95)	836 (20.78)	0.0030
<1 time/week	477 (18.14)	627 (15.59)	0.0482
1–2 times/week	637 (24.22)	992 (24.66)	0.0072
3–5 times/week	515 (19.58)	805 (20.01)	0.0076
5–7 times/week	450 (17.11)	763 (18.97)	0.0341
Smoking status	576 (15.89)	942 (19.72)	0.0708
Income/year (SEK), median (Q1, Q3)	199,638 (139,136, 261,558)	168,380 (121,840, 239,368)	0.1564
Marital status			
Married	2,518 (47.35)	2,227 (41.87)	0.0781
Separated	1,092 (20.53)	881 (16.56)	0.0723
Widowed	106 (1.99)	147 (2.76)	0.0358
Single	1,602 (30.12)	2,064 (38.80)	0.1297

Continued on p. 1279

Table 1—Continued

Characteristic	Group, *n* (%) or mean (SD)		Standardized difference
	GBP (*n* = 5,321)	Control (*n* = 5,321)	
Education			
Elementary school	1,069 (20.18)	1,431 (27.48)	0.1216
College level	3,192 (60.25)	2,847 (54.67)	0.0800
Upper secondary school	1,037 (19.57)	930 (17.86)	0.0311
Country			
Sweden	4,261 (80.08)	4,027 (75.68)	0.0750
Europe except Sweden	514 (9.66)	602 (11.31)	0.0382
Rest of world	546 (10.26)	692 (13.01)	0.0606

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; NSAID, nonsteroidal anti-inflammatory drug; Q, quartile; SEK, Swedish krona; SGLT2, sodium–glucose cotransporter 2.

with a Cox regression model adjusted for sex, age, BMI, eGFR, marital status, income, education, and country of birth. First- and 2nd-year postoperative clinical characteristics are described using descriptive statistics and compared between groups using ANCOVA and logistic regression models that included the baseline values as a covariate as appropriate. Missing values on variables, when used as confounders or risk factors in the Cox regression, are imputed using multiple imputation, creating 10 imputed data sets. When clinical variables are used as outcomes at 1 or 2 years, we use only observed values. Preexisting concomitant disease and preindex medications are captured without missing data. All *P* values were two-tailed, and those <0.05 were considered statistically significant.

RESULTS

We identified 5,321 patients from the SOReg with obesity who had undergone primary GBP and had T2DM. They were matched to 5,321 individuals with obesity and T2DM from the NDR between January 2007 and December 2015. The mean follow-up period for the GBP group was 4.7 years (range 0.02–9.0 years, lower quartile 3.6 years, upper quartile 5.8 years) and 4.6 years for the control group (range 0.02–9.7 years, lower quartile 3.3 years, upper quartile 5.8 years). At baseline (Table 1 and Supplementary Table 3), most characteristics were well balanced

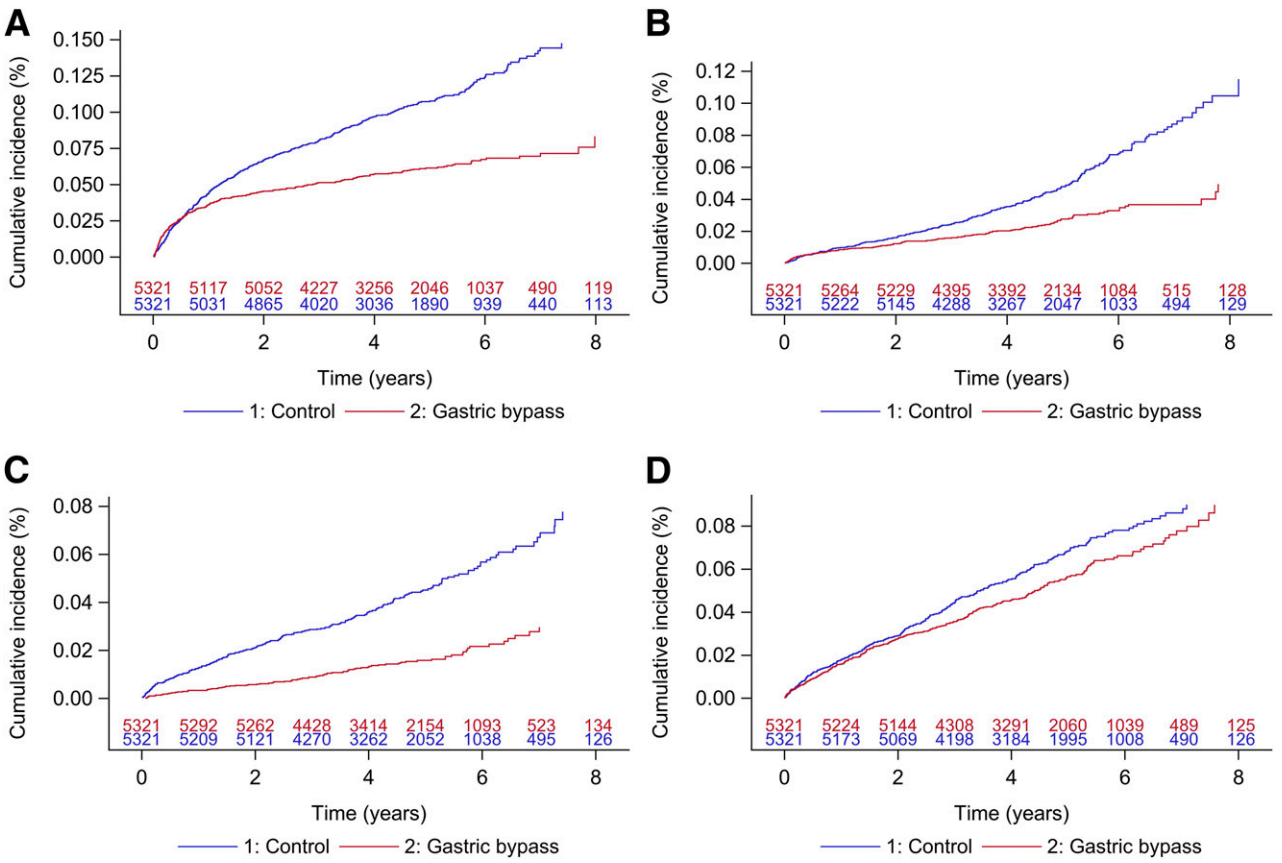

Figure 1—Cumulative incidence rates during the 9 years of follow-up. *A*: Macroalbuminuria. *B*: Severe renal disease or halved eGFR. *C*: Congestive heart failure. *D*: Nonfatal CVD.

Table 2—Number of events, incidence rate per 10,000 person-years by type, and adjusted HRs comparing GBP and matched control patients for sex, age, BMI, eGFR, and socioeconomic variables, including country of birth

End point	GBP (n = 5,321)	Control (n = 5,321)	HR (95% CI)	P value
Half eGFR (MDRD) (mL/min/1.73 m^2)	51 (20.43)	120 (49.00)	0.63 (0.45, 0.89)	0.0076
Half eGFR (CKD-EPI) (mL/min/1.73 m^2)	40 (16.02)	105 (42.86)	0.58 (0.40, 0.85)	0.0046
Macroalbuminuria	305 (127.22)	575 (252.33)	0.55 (0.47, 0.65)	<0.0001
Acute kidney failure	52 (20.85)	74 (30.14)	0.57 (0.36, 0.90)	0.0147
CKD	52 (20.84)	114 (46.62)	0.45 (0.30, 0.67)	0.0001
Diabetic nephropathy	17 (6.79)	53 (21.59)	0.22 (0.10, 0.47)	<0.0001
Severe renal disease	98 (39.49)	187 (76.87)	0.50 (0.37, 0.68)	<0.0001
Severe renal disease or half eGFR value (MDRD)	135 (54.57)	260 (107.39)	0.56 (0.44, 0.71)	<0.0001
Severe renal disease or half eGFR value (CKD-EPI)	124 (50.09)	245 (101.14)	0.54 (0.42, 0.70)	<0.0001
Hemodialysis or peritoneal dialysis	6 (2.39)	27 (10.97)	0.25 (0.08, 0.72)	0.0104
Kidney transplantation	6 (2.39)	6 (2.43)	0.62 (0.12, 3.39)	0.5854
Fatal kidney disease	12 (4.79)	32 (12.97)	0.48 (0.22, 1.04)	0.0636
CVD	291 (120.10)	346 (145.29)	0.74 (0.61, 0.89)	0.0015
Nonfatal CVD	286 (117.91)	333 (139.69)	0.82 (0.70, 0.97)	0.0184
Congestive heart failure	86 (34.56)	233 (96.40)	0.33 (0.24, 0.46)	<0.0001
Fatal CVD	31 (12.36)	93 (37.69)	0.36 (0.22, 0.58)	<0.0001
All-cause mortality	183 (72.90)	351 (142.06)	0.58 (0.47, 0.72)	<0.0001

after matching, except for minor differences where the standardized differences were >0.1. We found that patients in the GBP group had slightly higher age, BMI, income, education level, and consumption of analgesics (anti-inflammatories, opiates, etc.). The control group contained more unmarried patients. Among the GBP patients, the surgical procedures were laparoscopic in 96.0%, but 1.7% were initially laparoscopic and then converted to open surgery, while 2.3% used an open approach.

During the 1st and 2nd year of the follow-up period, there were marked reductions in BMI and HbA_{1c} as well as small reductions in serum creatinine, microalbuminuria, and macroalbuminuria in the GBP group (Supplementary Table 4). The eGFR levels were thus stable in this group, while there were small reductions in renal function in the control group. From the GBP group, 305 individuals developed macroalbuminuria as opposed to 575 in the control group, representing a 45% total risk reduction (Fig. 1*A*).

The incidence rates of almost all outcomes relating to renal function, CVD, and mortality were lower in the patients who had undergone GBP (Table 2). The incidence rates of severe renal diseases, consisting of several renal outcomes (Supplementary Table 1), were also lower (39.49 vs. 76.87 cases/10,000 person-years) in the GBP group. The incidence of a composite of severe renal disease or halved eGFR was 44% lower after GBP (0.56 [95% CI 0.44, 0.71]) (Table 2 and Fig. 1*B*). In this group, there was also a lower risk for CVD (nonfatal and fatal), congestive heart failure (Fig. 1*C*), and all-cause mortality (0.58 [0.47, 0.72]) as well as a lower mortality risk related to renal insufficiency (within 28 days after hospitalization as a result of a renal diagnosis) (0.48 [0.22, 1.04]) (Table 2). Notably, risks were markedly lower in the GBP group, especially for heart failure (HR 0.33 [95% CI 0.24, 0.46]) and CVD mortality (0.36 [0.22, 0.58]), whereas CVD risk (which combined nonfatal and fatal CVD) was less impressively lower at 0.74 (0.61, 0.89) and 0.82 (0.70, 097) for nonfatal CVD (Fig. 1*D*). There were no fatalities peroperatively, but two patients died on the 9th day after surgery, and one patient died after 13 days.

We compared number of renal and CV events and incidence rates at different levels of renal function (eGFR) in the two groups, adjusted for sex, age, and BMI (Table 3). Although there were some outcomes that were not statistically significantly lower in all eGFR strata, the overall pattern showed a clear risk reduction in individuals who had undergone GBP (i.e., even when eGFR was <45 or even <30 mL/min/1.73 m^2). To exemplify, the risk for severe renal disease or a 50% reduction in eGFR was 41% lower in patients with normal renal function and 63% and 60% lower in patients with eGFR 30–45 mL/min/1.73 m^2 and eGFR <30 mL/min/1.73 m^2, respectively, in those who had undergone GBP compared with those who had not. Similarly, the risks for congestive heart failure and fatal renal or CV events were also clearly lower after GBP in patients with the poorest renal function (Table 3).

CONCLUSIONS

Our observational study has three main findings. First, we showed a remarkable pattern of lower incidence of renal outcomes, such as development of diabetic nephropathy, impairment in renal function, and mortality related to renal function, even after a mean follow-up of 4.5 years after GBP in patients with T2DM relative to matched patients who had not undergone such surgical treatment. Second, we meaningfully extend the notion that large weight loss is more strongly linked to a lowering of risk for cardiorenal-related outcomes (i.e., renal disease, heart failure, CVD death) than it is for atherosclerotic disease (total CVD or nonfatal CVD), thereby elaborating a particular importance of obesity on cardiorenal pathways. Finally, we show that the observed benefits appear to be broadly consistent in individuals at all degrees of renal function, suggesting that "intentional" weight loss has the potential to lessen important risks even in patients with evident CKD. These findings, in turn, meaningfully extend our prior work in related areas (11,15,22).

Table 3—Number of events, incidence rate per 10,000 person-years by type, and adjusted HR compared with control patients, adjusted for sex, age, and BMI

End point	eGFR (mL/min/1.73 m^2)*	GBP	Control	HR (95% CI)	*P* value
Half eGFR (MDRD)	≥90	32 (33.59)	64 (49.63)	0.68 (0.44, 1.05)	0.0788
	90–60	11 (19.22)	31 (44.71)	0.47 (0.23, 0.95)	0.0356
	60–45	5 (93.88)	6 (70.42)	1.42 (0.40, 5.03)	0.5835
	45–30	1 (61.87)	11 (352.92)	0.13 (0.02, 1.03)	0.0538
	<30	2 (2.22)	8 (22.86)	0.10 (0.02, 0.49)	0.0046
Half eGFR (CKD-EPI)	≥90	18 (18.84)	36 (27.84)	0.69 (0.39, 1.22)	0.2039
	90–60	13 (22.74)	41 (59.32)	0.41 (0.22, 0.78)	0.0063
	60–45	5 (93.88)	7 (82.33)	1.26 (0.38, 4.21)	0.7110
	45–30	1 (61.87)	12 (386.52)	0.12 (0.02, 0.97)	0.0463
	<30	3 (3.33)	9 (25.73)	0.14 (0.04, 0.52)	0.0036
Macroalbuminuria	≥90	102 (110.48)	268 (221.22)	0.48 (0.38, 0.61)	<0.0001
	90–60	72 (130.93)	157 (244.41)	0.50 (0.38, 0.66)	<0.0001
	60–45	29 (661.83)	38 (504.37)	1.12 (0.68, 1.82)	0.6621
	45–30	14 (1,147.50)	32 (1,471.47)	0.81 (0.42, 1.56)	0.5245
	<30	88 (101.35)	80 (244.03)	0.39 (0.29, 0.53)	<0.0001
Acute kidney failure	≥90	7 (7.31)	25 (19.32)	0.36 (0.15, 0.83)	0.0168
	90–60	15 (26.27)	30 (43.25)	0.61 (0.32, 1.14)	0.1226
	60–45	3 (55.00)	6 (69.92)	0.94 (0.22, 3.98)	0.9321
	45–30	1 (60.42)	6 (190.21)	0.39 (0.04, 3.42)	0.3972
	<30	26 (29.07)	7 (19.96)	1.24 (0.54, 2.88)	0.6143
CKD	≥90	2 (2.09)	6 (4.63)	0.45 (0.09, 2.34)	0.3417
	90–60	11 (19.18)	28 (40.37)	0.48 (0.23, 0.97)	0.0424
	60–45	6 (110.87)	20 (241.33)	0.38 (0.15, 0.97)	0.0419
	45–30	6 (386.90)	28 (1,033.37)	0.29 (0.11, 0.71)	0.0074
	<30	27 (30.18)	32 (92.89)	0.28 (0.16, 0.47)	<0.0001
Diabetic nephropathy	≥90	2 (2.09)	14 (10.81)	0.22 (0.05, 0.99)	0.0485
	90–60	0	8 (11.51)	0.00 (0.00, —)	0.9930
	60–45	2 (36.33)	9 (106.71)	0.30 (0.06, 1.43)	0.1313
	45–30	1 (60.97)	8 (258.30)	0.19 (0.02, 1.61)	0.1286
	<30	12 (13.36)	14 (40.13)	0.34 (0.15, 0.75)	0.0079
Severe renal disease	≥90	10 (10.45)	30 (23.21)	0.42 (0.21, 0.88)	0.0204
	90–60	24 (42.15)	55 (79.83)	0.52 (0.32, 0.86)	0.0098
	60–45	10 (189.88)	28 (341.15)	0.51 (0.24, 1.07)	0.0754
	45–30	7 (453.82)	33 (1,281.85)	0.30 (0.13, 0.70)	0.0055
	<30	47 (52.96)	41 (119.43)	0.39 (0.25, 0.60)	<0.0001
Severe renal disease or half eGFR value (MDRD)	≥90	39 (40.99)	86 (66.96)	0.59 (0.41, 0.87)	0.0077
	90–60	29 (51.04)	72 (104.95)	0.51 (0.33, 0.79)	0.0024
	60–45	11 (211.45)	28 (342.66)	0.57 (0.28, 1.15)	0.1171
	45–30	8 (532.92)	33 (1,289.79)	0.37 (0.17, 0.83)	0.0153
	<30	48 (54.09)	41 (119.43)	0.40 (0.26, 0.61)	<0.0001
Severe renal disease or half eGFR value (CKD-EPI)	≥90	26 (27.25)	60 (46.59)	0.57 (0.36, 0.90)	0.0168
	90–60	31 (54.62)	81 (118.37)	0.48 (0.31, 0.73)	0.0006
	60–45	11 (211.45)	29 (355.70)	0.55 (0.27, 1.12)	0.1007
	45–30	8 (532.92)	34 (1,335.28)	0.36 (0.16, 0.80)	0.0120
	<30	48 (54.12)	41 (119.45)	0.40 (0.26, 0.61)	<0.0001
Hemodialysis or peritoneal dialysis	≥90	0	4 (3.08)	0.00 (0.00, —)	0.9958
	90–60	0	3 (4.30)	0.00 (0.00, —)	0.9957
	60–45	0	1 (11.60)	0.00 (0.00, —)	0.9986
	45–30	1 (60.68)	8 (254.26)	0.15 (0.02, 1.24)	0.0788
	<30	5 (5.55)	11 (31.47)	0.19 (0.06, 0.56)	0.0027

Continued on p. 1282

Table 3—Continued

End point	eGFR (mL/min/1.73 m^2)*	GBP	Control	HR (95% CI)	*P* value
CVD	≥90	81 (86.44)	133 (105.13)	0.73 (0.55, 0.96)	0.0260
	90–60	75 (135.04)	123 (184.82)	0.66 (0.49, 0.89)	0.0056
	60–45	17 (331.56)	23 (287.14)	1.11 (0.58, 2.12)	0.7494
	45–30	4 (259.25)	22 (778.56)	0.30 (0.10, 0.90)	0.0323
	<30	114 (131.96)	45 (131.42)	0.89 (0.62, 1.27)	0.5087
Congestive heart failure	≥90	21 (22.02)	71 (55.37)	0.35 (0.21, 0.57)	<0.0001
	90–60	15 (26.21)	83 (122.29)	0.22 (0.12, 0.38)	<0.0001
	60–45	6 (110.67)	29 (360.76)	0.33 (0.14, 0.82)	0.0165
	45–30	4 (250.82)	17 (569.27)	0.49 (0.16, 1.51)	0.2127
	<30	40 (44.83)	33 (95.41)	0.37 (0.23, 0.60)	<0.0001
Fatal kidney disease	≥90	1 (1.04)	5 (3.85)	0.34 (0.04, 3.13)	0.3396
	90–60	4 (6.96)	8 (11.46)	0.76 (0.21, 2.74)	0.6777
	60–45	0	2 (23.19)	0.00 (0.00, —)	0.9979
	45–30	1 (60.33)	6 (182.06)	0.34 (0.04, 2.96)	0.3317
	<30	6 (6.65)	11 (31.26)	0.18 (0.06, 0.50)	0.0010
Fatal CVD	≥90	8 (8.35)	32 (24.65)	0.30 (0.14, 0.66)	0.0026
	90–60	13 (22.62)	33 (47.27)	0.45 (0.23, 0.86)	0.0151
	60–45	0	12 (139.15)	0.00 (0.00, —)	0.9927
	45–30	1 (60.33)	4 (121.37)	0.48 (0.05, 4.62)	0.5287
	<30	9 (9.98)	12 (34.10)	0.28 (0.11, 0.70)	0.0066
All-cause mortality	≥90	57 (59.41)	136 (104.64)	0.53 (0.39, 0.72)	<0.0001
	90–60	54 (93.81)	108 (154.52)	0.65 (0.46, 0.91)	0.0115
	60–45	4 (71.93)	32 (370.51)	0.24 (0.08, 0.68)	0.0072
	45–30	4 (240.46)	24 (719.62)	0.40 (0.13, 1.19)	0.0996
	<30	64 (70.88)	51 (144.73)	0.35 (0.24, 0.51)	<0.0001

*Number of patients in the eGFR strata (GBP and control groups, respectively): eGFR ≥90 mL/min/1.73 m^2, 2,144 and 2,805; eGFR 90–60 mL/min/1.73 m^2, 1,274 and 1,493; eGFR 60–45 mL/min/1.73 m^2, 125 and 190; eGFR 45–30 mL/min/1.73 m^2, 35 and 79; and eGFR <30 mL/min/1.73 m^2, 1,743 and 754.

Obesity is an independent risk factor for CKD, as described in several studies (4–6,23). Similarly, the association of T2DM and renal impairment was reported in the UK Prospective Diabetes Study (UKPDS), with nearly 40% development of microalbuminuria and 30% development of renal disease over a median of 15 years from diagnosis of T2DM (24). Both factors promote an inflammatory status associated with infiltration of macrophages (7), activation of sympathetic nervous and renin-angiotensin systems followed by hypertension (25), and insulin resistance and associated hyperinsulinemia (leading to renal sodium retention) that may play a role in the pathophysiology of renal impairment (26). These mechanisms, and others related to hemodynamic perturbances in the context of obesity and diabetes (27), have been proposed as key to the development of glomerular hyperfiltration, glomerulopathy, and albuminuria. We believe that many of these perturbances, in particular hemodynamic pressures at the level of the nephron, are likely to be substantially attenuated by the sizeable weight loss achieved by GBP (11,28).

The remarkable pattern of potential benefits from GBP on renal, heart failure, and CVD mortality outcomes in T2DM mirror closely those of the sodium–glucose cotransporter 2 (SGLT2) inhibitor class and add support for obesity as a key factor leading to hemodynamic stress on relevant organ systems. The Swedish Obesity Subjects (SOS) study has suggested that improvements in various metabolic features (fat distribution, insulin resistance, glucose, HDL cholesterol, and triglycerides) likely predict improvement of albuminuria and renal function (29). A recent published retrospective study showed similar improvements on major CV events as well on heart failure, atrial fibrillation, and diabetic nephropathy (30). It is possible that renal benefits from significant weight loss arise from both the aforementioned conventional and novel (hemodynamic) pathways. Regardless of the responsible pathways, to put these results into context, very few therapies in the cardiometabolic space are known to slow the progression of renal dysfunction and development of heart failure to the extent suggested by our analyses. As mentioned, only SGLT2 inhibitors appear to similarly lessen such risks (31), leading to their further testing in ongoing renal outcome trials.

The findings of a retrospective study of 4,024 patients with T2DM, which investigated the relationship between bariatric surgery and the incidence of microvascular complications, defined as diabetic retinopathy, neuropathy, or nephropathy (eGFR <60 mL/min/1.73 m^2), showed lower cumulative incidence of nephropathy (i.e., a 59% lower risk) compared with nonsurgical patients at 5-year follow-up (32). However, they did not consider the entire spectrum of renal outcomes. Furthermore, a prospective case-control study in which 70 patients with T2DM underwent GBP presented a significant reduction of ACR for the 1st postsurgical year (33). The levels of albuminuria also improved in 77% of 101 patients with preoperative

diabetes, and albuminuria resolved in 51% of those who received bariatric surgery according to another retrospective study during a mean period of 61 months (34). Reviews and meta-analyses have also suggested beneficial effects of weight loss on albuminuria and bariatric surgery on albuminuria, impaired eGFR, creatinine, and other renal parameters (35).

Our study is based on two large registers (SOReg and NDR), with almost full coverage of Swedish patients who have T2DM and have undergone GBP. The validity of our data is reinforced by previous studies (19,36) and medical records, and the high power allows generalization of our results. The high quality of data for patients with obesity and T2DM increases the internal validity of the study, ensuring useful and reliable conclusions. We only examined, however, the effects of Roux-en-Y GBP and no other surgical methods, such as sleeve gastrectomy, since the former has been the dominant method during the study period, although the latter has been more widely used in recent years. It cannot be ruled out that the effects on renal function could differ to some extent between different surgical techniques, as suggested by the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial (12).

This observational retrospective cohort study included all patients with T2DM and GBP, but it was difficult to select control patients, especially younger ones. This explains the minor differences between the matched groups; we tried to eliminate them by adjusting our models for factors that were somewhat unbalanced. We cannot rule out the existence of potential residual confounding of unobserved factors. The effects of multiple comorbidities, which could also influence our results, were balanced between the groups, so we decided not to exclude them to preserve the power of our cohort. Other limitations were the decreasing proportion of data on postsurgical eGFR values as well as the absence of information on diagnoses not requiring hospitalization. The role of calculations that are based on serum creatinine values after reduction of muscle mass is being discussed (37); however, the pattern of results and their internal consistency, and their agreement with other epidemiological data strongly linking obesity to incident renal and heart failure outcomes, suggests that the pattern of our findings is likely to be broadly correct. It is also well known that obesity per se is a relatively modest risk factor for CVD, in particular nonfatal CVD (38).

Our work is important in underscoring the nature of a potential strong causal link of obesity to hard events (in particular cardiorenal outcomes), and we are not advocating that our results necessarily strengthen the case for more GBP per se. Indeed, it would be of interest to examine whether recent lifestyle interventions, which can lessen weight by ~7–10 kg per se for at least 1–2 years (39,40), can also lessen the risk for such outcomes in the longer term, provided that meaningful weight loss can be retained. Our work also strengthens the need to help people to prevent becoming obese in the first place.

In summary, on the basis of this nationwide observational study, we suggest that weight loss achieved by GBP contributes to lower risks of several diagnoses of renal disease and CVD and mortality in patients with obesity and T2DM and, importantly, does so across the full spectrum of baseline renal function, an important observation given that some patients with advanced renal disease could have their march toward dialysis substantially slowed. The pattern of results also adds support for the importance of obesity on the cardiorenal axis in particular. While the effects of bariatric surgery on renal function in obesity and T2DM remain to be confirmed in prospective trials, our findings add strong support for intentional weight loss as a legitimate intervention to prevent or delay renal dysfunction and related cardiac outcomes. Given the advent of newer drugs that can lower weight by ~10 kg, it would be important to see how such therapies affect relevant outcomes in the future.

Funding. This study was financed by the Swedish state under the agreement between the government and the county councils, the ALF agreement (235781), as well as grants from the Novo Nordisk Foundation and the Swedish Association of Local Authorities and Regions.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors contributed to the conception and design of the study and interpretation of the data. V.L. and B.E. drafted the manuscript. S.F. performed the statistical analyses. S.F., A.-M.S., M.M., J.O., and I.N. contributed to the acquisition of data. N.S., S.B., J.O., I.N., and S.G. contributed to critical revision. B.E. is the guarantor of this work and, as such, 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.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants [published correction appears in Lancet 2016;387:1998]. Lancet 2016;387:1377–1396
2. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271–281
3. Fenske W, Athanasiou T, Harling L, Drechsler C, Darzi A, Ashrafian H. Obesity-related cardiorenal disease: the benefits of bariatric surgery. Nat Rev Nephrol 2013;9:539–551
4. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk for chronic renal failure. J Am Soc Nephrol 2006;17:1695–1702
5. Vivante A, Golan E, Tzur D, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Arch Intern Med 2012;172:1644–1650
6. Chang Y, Ryu S, Choi Y, et al. Metabolically healthy obesity and development of chronic kidney disease: a cohort study. Ann Intern Med 2016;164:305–312
7. Maric-Bilkan C. Obesity and diabetic kidney disease. Med Clin North Am 2013;97:59–74
8. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery. J Intern Med 2013;273:219–234
9. Inge TH, Courcoulas AP, Jenkins TM, et al.; Teen-LABS Consortium. Weight loss and health status 3 years after bariatric surgery in adolescents. N Engl J Med 2016;374:113–123
10. Adams TD, Davidson LE, Litwin SE, et al. Weight and metabolic outcomes 12 years after gastric bypass. N Engl J Med 2017;377:1143–1155
11. Liakopoulos V, Franzén S, Svensson A-M, et al. Changes in risk factors and their contribution to reduction of mortality risk following gastric bypass surgery among obese individuals with type 2 diabetes: a nationwide, matched, observational cohort study. BMJ Open Diabetes Res Care 2017;5:e000386
12. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017;376:641–651
13. Mingrone G, Panunzi S, De Gaetano A, et al. 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 2015;386:964–973
14. Bruze G, Ottosson J, Neovius M, Näslund I, Marsk R. Hospital admission after gastric bypass: a nationwide cohort study with up to 6 years follow-up. Surg Obes Relat Dis 2017;13:962–969
15. Liakopoulos VFS, Svensson A-M, et al. Pros and cons of gastric bypass surgery in individuals with obesity and type 2 diabetes: nationwide, matched, observational cohort study. BMJ Open 2019;9:e023882

16. Logue J, Murray HM, Welsh P, et al. Obesity is associated with fatal coronary heart disease independently of traditional risk factors and deprivation. Heart 2011;97:564–568
17. Rosengren A, Åberg M, Robertson J, et al. Body weight in adolescence and long-term risk of early heart failure in adulthood among men in Sweden. Eur Heart J 2017;38:1926–1933
18. Eliasson B, Gudbjörnsdottir S. Diabetes care–improvement through measurement. Diabetes Res Clin Pract 2014;106(Suppl. 2):S291–S294
19. Hedenbro JL, Näslund E, Boman L, et al. Formation of the Scandinavian Obesity Surgery Registry, SOReg. Obes Surg 2015;25:1893–1900
20. Delanaye P, Mariat C. The applicability of eGFR equations to different populations. Nat Rev Nephrol 2013;9:513–522
21. Lu B. Propensity score matching with time-dependent covariates. Biometrics 2005;61:721–728
22. Eliasson B, Liakopoulos V, Franzén S, et al. Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nationwide, matched, observational cohort study. Lancet Diabetes Endocrinol 2015;3:847–854
23. Chang AR, Grams ME, Ballew SH, et al.; CKD Prognosis Consortium (CKD-PC). Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. BMJ 2019;364:k5301
24. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR; UKPDS Study Group. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes 2006;55:1832–1839
25. Hall ME, do Carmo JM, da Silva AA, Juncos LA, Wang Z, Hall JE. Obesity, hypertension, and chronic kidney disease. Int J Nephrol Renovasc Dis 2014;7:75–88
26. Tang J, Yan H, Zhuang S. Inflammation and oxidative stress in obesity-related glomerulopathy. Int J Nephrol 2012;2012:608397
27. Sattar N, McGuire DK. Pathways to cardiorenal complications in type 2 diabetes mellitus: a need to rethink. Circulation 2018;138:7–9
28. Amor A, Jiménez A, Moizé V, et al. Weight loss independently predicts urinary albumin excretion normalization in morbidly obese type 2 diabetic patients undergoing bariatric surgery. Surg Endosc 2013;27:2046–2051
29. Carlsson LM, Romeo S, Jacobson P, et al. The incidence of albuminuria after bariatric surgery and usual care in Swedish Obese Subjects (SOS): a prospective controlled intervention trial. Int J Obes (Lond) 2015;39:169–175
30. Aminian A, Zajichek A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA. 2 September 2019 [Epub ahead of print]. DOI: 10.1001/jama.2019.14231
31. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
32. O'Brien R, Johnson E, Haneuse S, et al. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. Ann Intern Med 2018;169:300–310
33. Miras AD, Chuah LL, Khalil N, et al. Type 2 diabetes mellitus and microvascular complications 1 year after Roux-en-Y gastric bypass: a case-control study. Diabetologia 2015;58:1443–1447
34. Young L, Nor Hanipah Z, Brethauer SA, Schauer PR, Aminian A. Long-term impact of bariatric surgery in diabetic nephropathy. Surg Endosc 2019;33:1654–1660
35. Li K, Zou J, Ye Z, et al. Effects of bariatric surgery on renal function in obese patients: a systematic review and meta analysis. PLoS One 2016;11:e0163907
36. Emilsson L, Lindahl B, Köster M, Lambe M, Ludvigsson JF. Review of 103 Swedish healthcare quality registries. J Intern Med 2015;277:94–136
37. Chuah LL, Miras AD, Perry LM, et al. Measurement of glomerular filtration rate in patients undergoing obesity surgery. BMC Nephrol 2018;19:383
38. Wormser D, Kaptoge S, Di Angelantonio E, et al.; Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011;377:1085–1095
39. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol 2019;7:344–355
40. Astbury NM, Aveyard P, Nickless A, et al. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. BMJ 2018;362:k3760